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Efficacy of Immunotherapy in Patients With Bone Metastases From Driver Gene-Negative Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: This study systematically assesses the efficacy of immunotherapy as a first-line treatment for patients with non-small-cell lung cancer (NSCLC) and bone metastases who lack driver gene mutations. This analysis draws on data from randomized controlled trials to support individualized treatment strategies.

Methods: Randomized controlled trials published up to October 1, 2024, were retrieved from PubMed, EMBASE, the Cochrane Library, and the Web of Science. Statistical analyses were conducted using RevMan 5.4 and STATA 17.0, with the results presented in forest plots. Progression-free survival (PFS) and overall survival (OS) were analyzed using hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024604768).

Results: Meta-analysis demonstrated a significant improvement in OS and PFS for patients with bone metastases receiving immunotherapy (OS: HR: 0.81, 95% CI: 0.71-0.92; PFS: HR: 0.78, 95% CI: 0.62-0.98). Although the survival benefit of immunotherapy was lower in patients with bone metastases than in those without, it was superior to chemotherapy.

Conclusions: Among patients with driver gene-negative NSCLC and bone metastases, immunotherapy significantly improved OS and PFS, thus supporting its role as an effective first-line treatment. Further large-scale trials are recommended to enhance treatment precision and validate these findings.

Keywords

Non-small-cell lung cancer, immune checkpoint inhibitor, chemotherapy, bone metastasis, first-line therapy

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Introduction

Lung cancer accounts for a significant proportion of the global cancer burden and is one of the leading causes of cancer-related deaths worldwide due to its high invasiveness and prevalence.[1] Non-small-cell lung cancer (NSCLC), which comprises approximately 82% of all lung cancers, generally progresses more slowly than other types. However, approximately 40% of patients with NSCLC are diagnosed at advanced stages, often with metastases, significantly reducing survival rates.[2] Advancements in tumor immunology have revolutionized NSCLC treatment, particularly through

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the introduction of immune checkpoint inhibitors (ICIs) for patients without driver gene mutations. For instance, the KEYNOTE-024 study found that patients with NSCLC and programmed death-ligand 1 (PD-L1) expression ⩾ 50% who received pembrolizumab had significantly longer progression-free survival (PFS) and overall survival (OS) than those receiving chemotherapy, with fewer adverse events.[3]

This finding led the US Food and Drug Administration (FDA) to approve pembrolizumab as a first-line monotherapy for patients with NSCLC and high PD-L1 expression.[4] Despite its promising efficacy, PD-1/PD-L1 monotherapy is less effective in patients with low or negative PD-L1 expression, thus increasing interest in combination therapies.

The KEYNOTE-189 study[5] demonstrated that combining pembrolizumab with chemotherapy (carboplatin and pemetrexed) significantly improved PFS and OS across various PD-L1 expression levels. For instance, in the pembrolizumab-combination group, 12-month OS (22.0 vs 10.6 months) and PFS (8.8 vs 4.9 months) were notably higher than in the chemotherapy-only group. This prompted the FDA to approve non-squamous NSCLC in May 2017 and squamous NSCLC in October 2018. Furthermore, in 2020, the FDA approved a combination of nivolumab and ipilimumab with 2 cycles of platinum-based chemotherapy as a first-line treatment for metastatic NSCLC based on findings from the CheckMate-9LA study.[6,7] These advances have firmly positioned ICIs as the cornerstone of advanced NSCLC treatment and fundamentally shifted the therapeutic approach for patients without driver gene mutations.[8,9]

Despite advancements in immunotherapy for advanced NSCLC, OS remains relatively low, with a 5-year survival rate of only 19%.[10] Research suggests that metastases significantly affect survival outcomes in NSCLC, with bone metastases among the most prevalent and affecting 20% to 40% of patients.[11-13] Bone metastases cause severe pain and pathological fractures and lead to skeletal-related events (SREs), including spinal cord compression and hypercalcemia, which significantly reduce patients' quality of life and survival rates.[14,15] Current treatments for bone metastases primarily include palliative radiotherapy, bisphosphonates, and bone-targeting therapies such as denosumab.[16] However, their effectiveness in improving survival rates is limited.

Radiotherapy outcomes depend on factors such as dose, treatment site, and individual patient differences, with repeated sessions posing risks of bone marrow suppression and tissue damage. Bone-targeting therapies primarily reduce SREs and improve quality of life. However, as many patients with bone metastases are in advanced stages and have limited time for bone remodeling, the survival benefit of these therapies remains minimal.[12,17,18]

Evidence suggests that bone marrow actively regulates immune function and immune cell trafficking. The immunosuppressive microenvironment of bone tissue fosters an immune-inhibitory state within the tumor microenvironment, which is mediated by suppressive immune cells and signaling molecules.[19] Immune checkpoint inhibitors can counteract these effects by restoring T-cell activity to enhance antitumor immune responses, reduce tumor burden, and limit cancer spread within bone tissue.

During bone metastasis, increased osteoclast activity accelerates bone degradation, whereas suppressed osteoblast activity contributes to bone destruction. Immunotherapy helps restore this balance by activating T cells, which regulate interactions between osteoclasts and osteoblasts, ultimately reducing bone tissue degradation.[20] Given the key mechanisms under which immunotherapy affects bone metastases, recent studies have investigated the use of ICIs to improve patients with NSCLC, bone metastases, and no driver gene mutations.

In a retrospective study, Li et al[21] reported that bone metastases negatively affect the efficacy of ICI monotherapy in patients with NSCLC, thus significantly reducing both PFS and OS. Bone metastases are a prognostic factor associated with poor clinical outcomes in patients with lung cancer treated with ICIs. However, the JAVELIN Lung100 study[22] found that ICI treatment significantly improves PFS and OS in patients with advanced, driver gene-negative NSCLC and bone metastases.

Similarly, the CheckMate 227 Part 1 study[23] showed that immunotherapy significantly prolonged the OS of patients with bone metastases. Overall, multiple studies suggest that ICIs may improve OS and PFS in driver gene-negative advanced NSCLC, particularly in cases with extensive metastases. However, the efficacy and safety of ICIs in patients with bone metastases remain poorly understood, with the incidence and severity of immune-related adverse events requiring careful evaluation. Therefore, a comprehensive meta-analysis is essential to systematically assess the efficacy and safety of immunotherapy as a first-line treatment for driver gene-negative NSCLC in patients with bone metastases.

This meta-analysis employed rigorous literature search and data selection criteria to ensure scientifically valid and reliable results. By systematically evaluating the OS and PFS, we provide empirical evidence to support clinical decision-making. Furthermore, this study explored the therapeutic potential and limitations of combining immunotherapy with chemotherapy and offers a foundation for personalized treatment strategies for patients with NSCLC and bone metastases lacking driver gene mutations.

Materials and methods

Search strategy

Following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[24] we conducted a systematic literature search using a prespecified protocol. As of October 1, 2024, we searched 4 major databases (PubMed, EMBASE, Cochrane Library, and Web of Science) for randomized controlled trials (RCTs) on immunotherapy in advanced NSCLC, thus limiting the results to English-language publications. We also reviewed references of relevant articles and abstracts from major conferences, including the American Society of Clinical Oncology (ASCO), World Conference on Lung Cancer (WCLC), European Society for Medical Oncology (ESMO), and American Association for Cancer Research

(were). The search incorporated free text and MeSH terms combined with Boolean operators (AND/OR).

The key search terms included "pembrolizumab," "nivolumab," "atezolizumab," "durvalumab," "avelumab," "sugemalimab," "toripalimab," "immune checkpoint inhibitors," "NSCLC," "non-small cell lung cancer," "metastasis," and "advanced." The detailed search strategies for each database are presented in Supplementary Material 1. Duplicate records were removed before analysis of the remaining articles. Two researchers independently screened the studies, beginning with titles and abstracts, followed by a full-text review. A third researcher mediated disagreements until consensus was reached. The reference lists of the eligible studies were screened for additional relevant articles. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024604768.

Inclusion and exclusion criteria

Inclusion criteria. Studies were selected based on the population, intervention, comparison, outcomes and study (PICOS) framework. Population (P): patients diagnosed with NSCLC with bone metastases. Intervention (I): studies comparing an experimental and a control group. The experimental group received immunotherapy-based treatment, with or without additional drugs, whereas the control group received chemotherapy or a placebo. Outcomes (O): Studies reporting PFS and OS data stratified by bone metastasis status (presence or absence), with associated hazard ratios (HRs). Progression-free survival was defined as the time from randomization to the first progression (local or distant) or death, and OS was defined as the time from randomization to death from any cause. Study design (S): Only RCTs were included in this meta-analysis.

Exclusion criteria. Studies were excluded based on the following criteria: (1) absence of OS and PFS data based on bone metastasis status; (2) study type limitations, including reviews, abstracts, case reports, letters, animal studies, and retrospective studies; (3) incomplete or unclear survival data affecting result interpretation; and (4) incorrect statistical methods or missing HRs and 95% CIs that could not be calculated or converted. For duplicate clinical trials, the most recent or most complete dataset was used. Two authors independently reviewed the final results, and specific study disagreements were resolved through consensus discussions among all researchers.

Data extraction

The following information was extracted from each study: title, author(s), publication year, study phase, intervention and control measures, sample sizes for both groups, and HRs for PFS or OS with corresponding 95% CIs for patients with and without bone metastases. For studies reporting multiple datasets, the most recent or most complete dataset was used.

Quality and bias assessment

The quality of RCTs was assessed using the Cochrane risk of bias 2 (RoB 2) tool,[25] which evaluates 5 key domains: (1) bias from the randomization process, (2) bias due to deviations from intended interventions, (3) missing outcome data, (4) bias in outcome measurement, and (5) bias in selecting reported results.

Statistical analysis

Statistical analyses were conducted using RevMan 5.4 and STATA 17.0, with results presented in forest plots. Progression-free survival and OS were analyzed using HRs with corresponding 95% CIs. Heterogeneity was assessed using the I^2 test: an $I^2 \leqslant 50\%$ indicated low heterogeneity, warranting the use of a fixed-effects model, whereas an $I^2 > 50\%$ indicated significant heterogeneity, prompting the use of a random-effects model. Funnel plots were constructed based on the number of studies in the PFS and OS analyses. Publication bias was evaluated using Begg and Egger tests. Sensitivity analyses were performed to assess the robustness of the results, with $P < .05$ considered statistically significant.

Results

Literature search

The initial search yielded 17 439 articles. After removing 2672 duplicates, 6874 studies were excluded for not being RCTs. Screening titles and abstracts led to the exclusion of 5326 studies that were not relevant. Full-text reviews were conducted on the remaining 2576 potentially eligible articles. Following the inclusion and exclusion criteria, 8 RCTs,[22,23,26-31] were included in the final analysis. Figure 1 illustrates the literature selection process.

Study characteristics

All included studies were phase III RCTs, with patient diagnoses based on the tumor-node-metastasis (TNM) staging criteria for NSCLC, thus focusing on advanced or metastatic stages. The intervention group received ICI-based antitumor therapy, whereas the control group was treated with non-ICI chemotherapy regimens, with ICIs administered as the first-line treatment. Seven RCTs[22,23,26,27,29-31] included patients with NSCLC regardless of histological subtype, whereas 1 study[28] specifically focused on patients with non-squamous cell carcinoma. Each study reported an association between bone metastasis and OS or PFS, with some provided OS or PFS data for patients without bone metastases. Table 1 presents the study characteristics.

Quality assessment of included studies

The RoB in the included RCTs was assessed using the RoB 2 tool across the 5 domains. Three studies were classified as having a low RoB. Several studies had an unclear RoB due to insufficient reporting of specific methodological details,

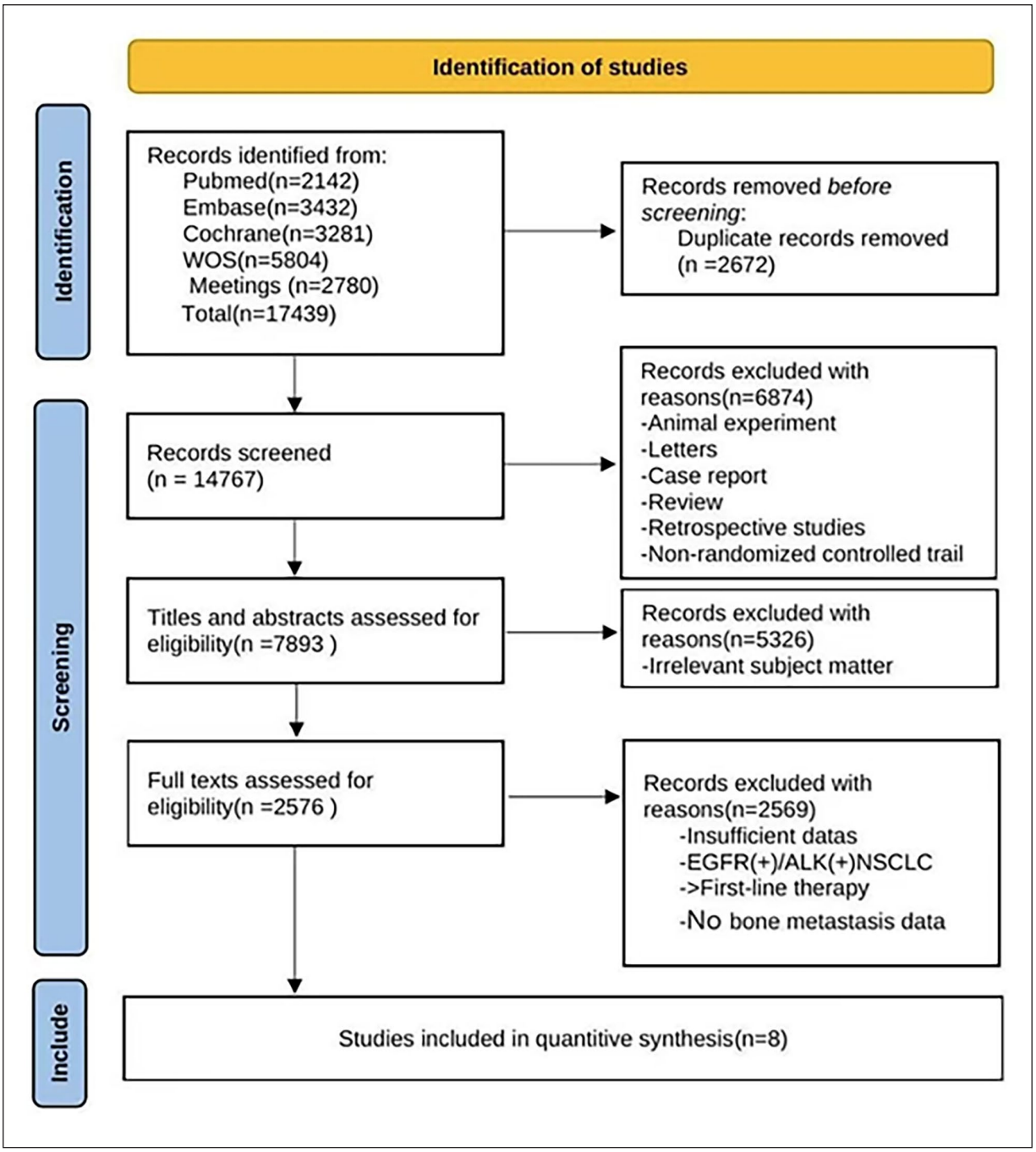

Figure 1. The flow chart of search and study collection.

whereas none were classified as high risk. Overall, the included studies demonstrated a low RoB (Figure 2).

Meta-analysis results

A meta-analysis was conducted to assess the efficacy of immunotherapy in the bone metastasis subgroup across all included studies. Forest plots from the meta-analysis indicated that immunotherapy significantly improved OS and PFS than chemotherapy-based non-ICI strategies. For OS, heterogeneity analysis showed low heterogeneity ($P = .20$, $I^2 = 29\%$), thus confirming the use of a fixed-effects model. The combined analysis demonstrated that immunotherapy significantly improved OS in patients with NSCLC and bone metastases who lacked driver gene mutations (HR: 0.81, 95% CI: 0.71-0.92), with a statistically significant difference (Figure 3A).

Five studies provided data on PFS, with no observed heterogeneity; therefore, a fixed-effects model was used. As shown in the forest plot (Figure 3B), immunotherapy-based treatments significantly outperformed chemotherapy-based regimens regarding PFS (HR: 0.78; 95% CI: 0.62-0.98). These results suggest a survival advantage of immunotherapy in patients with bone metastases. In addition, 6 studies reported OS outcomes for patients with NSCLC without bone metastases (Figure 3C). The findings

Table 1. Baseline characteristics of the included studies.

Study	Year	Author	Phase	Bone metastasis no.(I/C)	Non-bone metastasis no.(I/C)	Histology	PD-L1	TMB	Intervention	Control treatment	OS HR (95% CI)	PFS HR (95% CI)
JAVELIN Lung 100a	2023	Martin Reck	III	28/49	122/165	Sq or no-sq	PD-L1 ⩾ 80%	NA	Avelumab(Q2W)	CT(gem + ddp or cbp/ptx + cbp/pem + cbp or ddp)	0.81 (0.49-1.33)	0.65 (0.37-1.15)
JAVELIN Lung 100b	2023	Martin Reck	III	40/30	90/98	Sq or no-sq	PD-L1 ⩾ 80%	NA	Avelumab(QW)	CT(gem + ddp or cbp/ptx + cbp/pem + cbp or ddp)	0.56 (0.32-0.99)	0.64 (0.35-1.19)
ONO-4538-52/ TASUKI-52	2023	Hye Ryun Kim	III	56/83	219/192	no-sq	PD-L1 < 1%, 1%-49%, or ⩾ 50%	NA	Nivolumab + Bevacizumab + CT	Bev + CT (ptx + cbp)	1.03 (0.66-1.59)	0.87 (0.56-1.37)
CheckMate 227 Part 1	2022	LuisG. Paz-Ares	III	163/153	420/430	Sq or no-sq	PD-L1 < 1% or ⩾ 1%	TMB < 10 or ⩾ 10	Nivolumab + Ipilimumab	CT(cbp + ddp)	0.68 (0.53-0.87)	-
CheckMate 9LA	2024	Martin Reck	III	97/111	264/247	Sq or no-sq	PD-L1 < 1%, ⩾ 1%, 1%-49%, or ⩾ 50%	NA	Nivolumab + Ipilimumab + CT	CT(pem/gem + cbp or ddp	0.74 (0.560.99)	-
CHOICE-01	2022	Zhijie Wang	III	92/46	217/110	Sq or no-sq	PD-L1 < 1% or ⩾ 1%	TMB < 10, ⩾ 10 or NA	Toripalimab + CT	CT(nab-p + cbp/pem + ddp or cbp)	0.84 (0.52-1.37)	0.69 (0.45-1.06)
CheckMate 227 Part 2	2023	H. Borghaei	III	108/120 82/86	269/258 188/187	Sq or no-sq no-sq	PD-L1 < 1%, ⩾ 1%, or ⩾ 50%	TMB < 10 or ⩾ 10	Nivolumab + CT	CT(ptx + cbp/pem + cbp or ddp)	0.97 (0.72-1.31) 0.99 (0.69-1.40)	- -
BFAST cohort C	2022	Solange Peters	III	34/30	111/116	Sq or no-sq	NA	TMB ⩾ 16	Atezolizumab + CT	CT(pem/gem + cbp or ddp)	1.40 (0.77-2.53)	1.15 (0.66-2.00)

Abbreviations: Bev, bevacizumab; cbp, carboplatin; CI, confidence interval; CT, chemotherapy; ddp, cisplatin; no-sq, non-squamous; GEM, gemcitabine; HR, hazard ratio; NA, not available; nab-p, nab-paclitaxel; OS, overall survival; PD-L1, programmed death-ligand 1; pem, pemetrexed; PFS, progression-free survival; ptx, paclitaxel; Sq, squamous; TMB, tumor mutational burden.

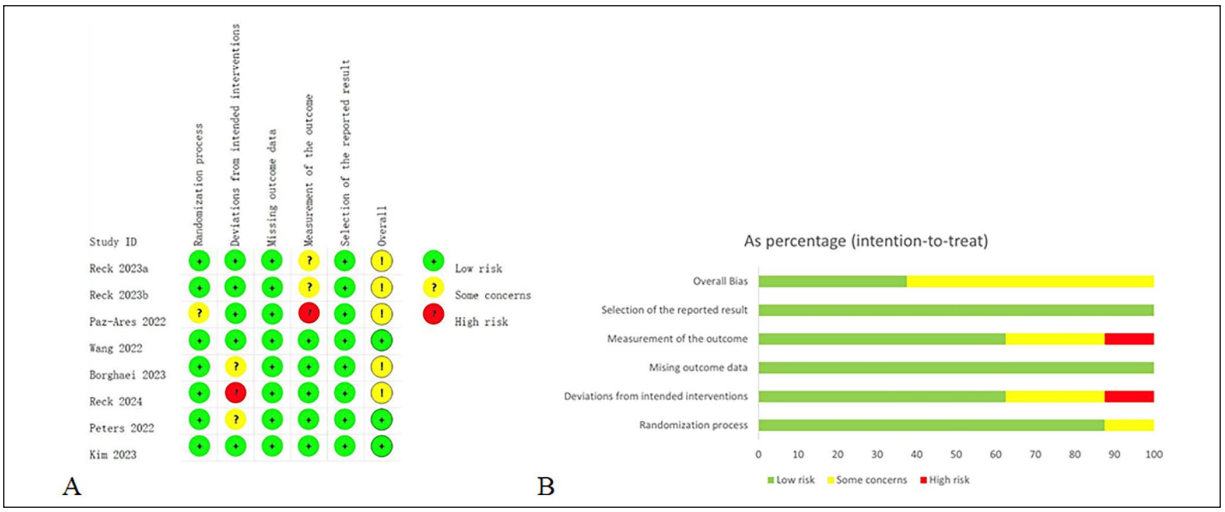

Figure 2. Quality assessment of the included studies. (A) The details of bias assessment. (B) The summary of bias assessment.

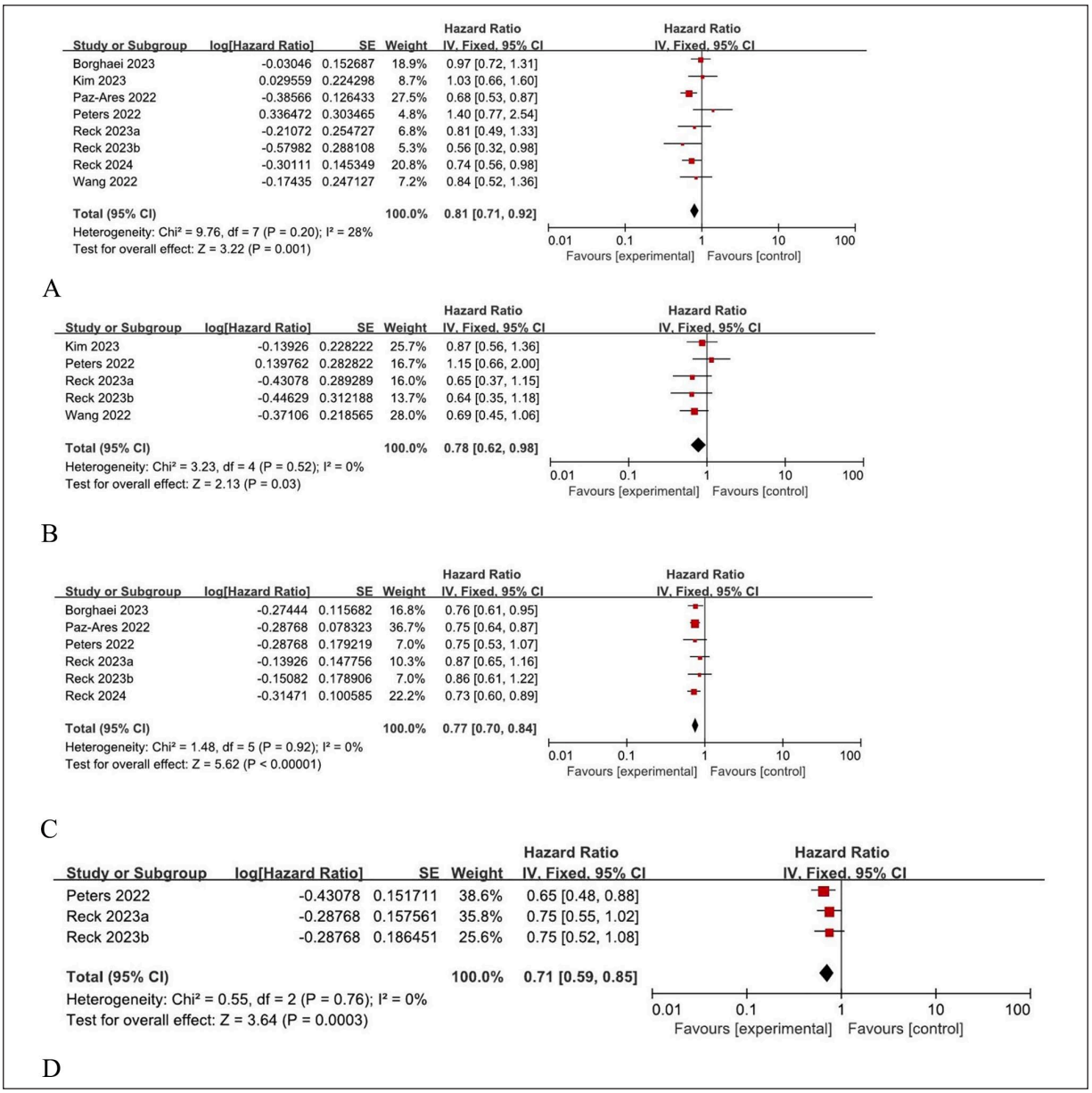

Figure 3. Forest plot comparing OS and PFS. (A) OS in patients with bone metastases. (B) PFS in patients with bone metastases. (C) OS in patients without bone metastases. (D) PFS in patients without bone metastases.

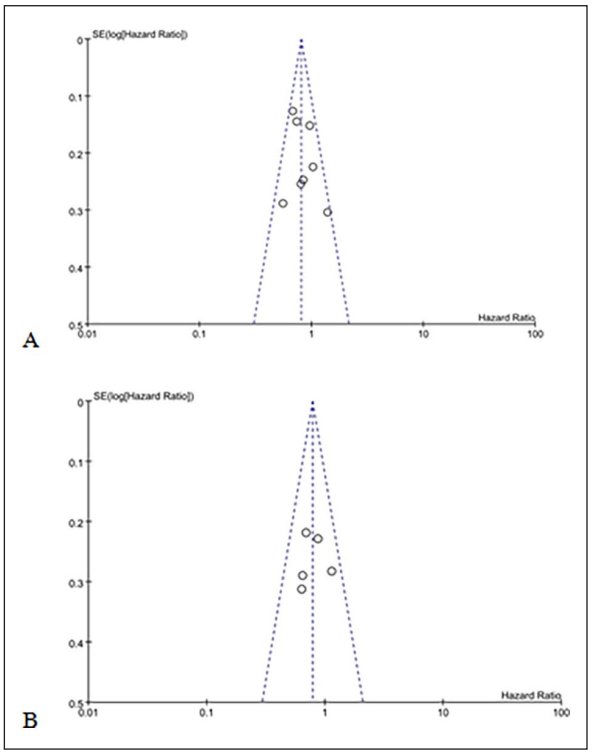

Figure 4. Funnel plot for the meta-analysis of bone metastasis on OS (A) and PFS (B) in patients with NSCLC.

indicated that immunotherapy was significantly more effective than chemotherapy in improving OS (HR: 0.77, 95% CI: 0.70-0.84). Progression-free survival outcomes were reported in 3 studies, where immunotherapy also showed a survival advantage over chemotherapy (HR: 0.71, 95% CI: 0.59-0.85), with a statistically significant difference (Figure 3D).

Among patients with driver gene-negative NSCLC, those without bone metastases experienced significant improvements in OS and PFS with immunotherapy than those with bone metastases. These findings suggest that patients without bone metastases may derive significant benefits from immunotherapy. This highlights the need for optimizing subgroup-specific immunotherapy regimens in future clinical practice. Although the survival benefits are less pronounced in patients with bone metastases, immunotherapy remains an effective treatment option.

Sensitivity analysis

Sensitivity analyses were conducted for PFS and OS by sequentially excluding each study to evaluate its impact on the overall results. The findings showed that removing any single study did not significantly affect the pooled effect estimates (Supplementary Figure 1), thus confirming the robustness of the results and the absence of undue influence from any individual study.

Publication bias

Publication bias for the PFS and OS outcomes related to bone metastases was assessed. Funnel plots of PFS and OS (Figure 4) showed a visually symmetrical distribution, which indicated a low risk of publication bias. Given the limited number of studies, Begg and Egger tests were conducted at a significance level of $P < .05$. Neither test showed a significant publication bias. Detailed results of the Egger and Begg tests are presented in Supplementary Table 1.

Discussion

The bone is one of the most common metastatic sites in NSCLC, and its presence is typically associated with significantly reduced survival.[32] Despite advancements in treatment, including bone-targeted therapies and immunotherapy, patient outcomes remain suboptimal. Therefore, it is essential to evaluate the efficacy of immunotherapy in patients with NSCLC and bone metastases without driver gene mutations and identify factors influencing treatment outcomes.

To our knowledge, this meta-analysis consolidates the largest number of phase III RCTs evaluating immunotherapy for patients with NSCLC and bone metastases without driver gene mutations. Our rigorously conducted analysis demonstrates that immunotherapy improves PFS and OS in patients, regardless of bone metastasis status. Moreover, patients without bone metastases derive significant survival benefits from immunotherapy than those with bone metastases.

Several studies have identified bone metastasis as an independent predictor of a poor prognosis following immunotherapy. Landi et al[33] conducted a retrospective cohort study to assess the effect of bone metastasis on the efficacy of immunotherapy in patients with advanced NSCLC by focusing on the ICI nivolumab. Their findings revealed that regardless of the histological subtype (squamous or nonsquamous cell carcinoma), patients with bone metastasis had significantly lower PFS and OS than those without the condition.

Multivariate analysis further demonstrated a significant association between the bone metastasis and increased mortality risk. Similarly, Li et al[21] found that, within the ICI monotherapy group, patients with bone metastases experienced shorter PFS (4.2 vs 6.7 months, $P = .048$) and OS (12.5 vs 23.9 months, $P = .004$) than those without bone metastases. In contrast, the presence of bone metastases did not significantly affect the PFS or OS in patients receiving combination therapy. These findings suggest that bone metastasis may reduce the efficacy of ICI monotherapy in patients with advanced NSCLC; however, combination therapy may help mitigate this adverse effect. A retrospective study by Qiang et al[34] examined the efficacy of pembrolizumab, administered either as a monotherapy or in combination, in patients with advanced NSCLC with bone metastases. This study analyzed 110 patients with advanced NSCLC and found that pembrolizumab was effective in this population, with notably improved outcomes in patients receiving concurrent bone-targeted therapies. In addition, patients with solitary bone metastases demonstrated significantly longer survival than those with multiple bone metastases. Baseline levels of lactate dehydrogenase and the neutrophil-to-lymphocyte ratio were identified as

potential biomarkers for predicting the prognosis of patients with bone metastases.

The previous sections have briefly discussed the mechanisms underlying the role of bone metastasis as a prognostic factor in immunotherapy, including the immunosuppressive characteristics of the bone microenvironment. The bone marrow harbors a significant population of immunosuppressive cells, including regulatory T cells and myeloid-derived suppressor cells, which inhibit the immune clearance of tumor cells. In addition, osteoclasts contribute to an immunosuppressive "cold" tumor microenvironment by releasing molecules such as indoleamine 2,3-dioxygenase-1 (IDO1), interleukin 10 (IL-10), and transforming growth factor-β (TGF-β), thereby suppressing T-cell antitumor activity. The "vicious cycle" mechanism involves tumor cell-derived factors, such as parathyroid hormone–related peptide (PTHrP) and prostaglandin E2 (PGE2), which promote osteoclast formation, leading to bone resorption and a tumor-supportive microenvironment.[33,35,36]

The limited efficacy of immunotherapy observed in the studies discussed may be partly due to small sample sizes and potential study biases. Furthermore, combination immunotherapy may help improve bone metastatic tumors and enhance the effectiveness of immunotherapy. Based on these insights, a comprehensive treatment strategy targeting bone metastases may optimize immunotherapy outcomes for patients with NSCLC with bone metastases in future clinical applications.

Recently, several meta-analyses examined the relationship between bone metastasis in NSCLC and the efficacy of ICIs. A systematic review and meta-analysis published in 2023[37] found a significant association between bone metastases and poor OS (HR: 1.55, 95% CI: 1.24-1.94), indicating reduced survival in patients with bone metastases. However, in the PFS analysis, bone metastases did not demonstrate a significant impact (HR: 1.31, 95% CI: 0.85-2.01), suggesting no strong association between bone metastasis and tumor progression rate. In another meta-analysis by Huang et al,[38] patients with bone metastases receiving PD-1 inhibitors showed significantly reduced OS with an increased risk of death (HR: 1.67, 95% CI: 1.30-2.16).

Similar to previous studies, bone metastasis did not significantly affect PFS ($P > .05$), indicating that there was no strong association between bone metastasis and the rate of tumor progression. These findings suggest that bone metastasis is associated with poor OS in patients with advanced NSCLC receiving PD-1 inhibitor therapy, highlighting its role as a critical adverse prognostic factor. However, most studies included in these meta-analyses were retrospective, potentially introducing a selection bias that may have affected the results. While previous meta-analyses have demonstrated that bone metastasis is associated with reduced efficacy of immunotherapy compared to non-bone metastasis subgroups,[37,38] our study provides critical evidence that immunotherapy remains superior to chemotherapy in patients with bone metastasis, albeit with an attenuated benefit. These findings underscore the necessity of distinguishing between prognostic factor analysis and therapeutic efficacy comparison; as bone metastasis is associated with attenuated immunotherapy benefit (prognostic effect), it does not diminish the superiority of immunotherapy over chemotherapy in this subgroup.

In addition, unlike previous meta-analyses, our study specifically focused on patients without driver gene mutations, which allowed us to exclude the confounding effects of these mutations and gain a clearer understanding of the role of immunotherapy in this distinct patient subgroup. The potential mechanisms underlying these findings are as follows: (1) Higher tumor mutational burden (TMB): Patients with NSCLC without driver gene mutations generally exhibit a higher TMB, which causes an increased neoantigen production that activates antitumor immune responses. High TMB is closely associated with enhanced efficacy of ICIs, such as PD-1/PD-L1 inhibitors.[39] (2) More immunogenic tumor microenvironment: The tumor microenvironment in patients without driver genes tends to be more immunogenic, with higher T-cell infiltration and elevated PD-L1 expression. These characteristics enhance the action of ICIs and enable the immune system to more effectively recognize and eliminate tumor cells.[40] (3) Immune suppression in driver-positive patients: Certain driver-positive patients (eg, those with epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase mutations) experience immune suppression because of the activation of specific signaling pathways. For example, EGFR mutations can upregulate PD-L1 expression, inhibit the immune response, and reduce the effectiveness of immunotherapy. Conversely, patients without driver genes are less affected by these inhibitory mechanisms, thus resulting in better immunotherapy outcomes.[41] (4) Pro-inflammatory pathway activation: Tumor cells in patients without driver genes may activate pro-inflammatory pathways that enhance the sensitivity of the tumor microenvironment to immunotherapy and increase its antitumor efficacy.[42]

Our findings suggest that immunotherapy is a promising first-line treatment for patients with NSCLC with bone metastases who lack driver gene mutations. However, these results should be interpreted with caution to avoid overestimating the role of immunotherapy in this specific population. Future large-scale clinical trials are necessary to further investigate optimal first-line immunotherapy regimens for this patient subgroup.

Our study had several limitations. First, the analysis was based on data from published RCTs rather than individual patient data. While our meta-analysis represents the largest synthesis of RCT data to date in this population, the absolute number of bone metastasis-specific cases remains limited compared with broader NSCLC trials. This reflects the inherent challenge of recruiting homogeneous subgroups for global RCTs. Second, the included studies employed different immunotherapy agents, potentially introducing heterogeneity in treatment protocols and increasing result variability. Third, the lack of sufficient blinding in several studies may have led to a selection bias, lowering the quality of evidence. Fourth, due to the limited number of included studies, we were unable to conduct subgroup analyses based on histological type, specific immunotherapy

protocols, differences between multiple and solitary bone metastases, or the presence of multiorgan metastasis alongside bone metastasis.

Conclusions

Overall, our analysis of RCTs suggests that patients with driver gene-negative NSCLC and bone metastases should not be excluded from ICI treatment, despite the potentially lower OS and PFS benefits compared with patients without bone metastases. These findings may help clinicians optimize treatment strategies for this patient group. However, given the limited number of studies, our results should be interpreted with caution and validated in future clinical trials. In addition, exploring additional combination treatment strategies in clinical practice is crucial for improving patient prognosis.

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Author Contributions

Weixing Zhao and Xiaoni Jin: Writing the original draft and conceptualization. Bo Li: Methodology. Yujia Gu: Formal analysis. Zirui Li: Formal analysis. Wanjing Guo: Supervision. Xinxin Lu: Resources. Jun Jiang: Writing-review and editing, funding acquisition.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

Availability of data and materials All study data are included in the published article.

Supplemental Material

Supplemental material for this article is available online.

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