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Meta-analysis of the efficacy and safety of bispecific antibodies in immune therapy for lung cancer.

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Keywords: Antibodies; Bispecific; Lung cancer; Immunotherapy; Meta-Analysis; Efficacy; Safety.

Abstract. This work evaluates the efficacy and safety of bispecific antibodies (BsAbs) in lung cancer immunotherapy through a meta-analysis, providing more comprehensive evidence for their clinical application. A systematic search was conducted in PubMed, Embase, Cochrane Library, and various Chinese databases to identify eligible randomized controlled trials and quasi-randomized controlled trials. Clinical data on bispecific antibody therapy for lung cancer were collected. The primary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and the incidence of immune-related adverse events (irAEs). Data analysis was performed using RevMan 5.3 software, with fixed-effect or random-effects models. Nine studies were included, with a total sample size of 588 patients. The meta-analysis revealed no statistically significant differences between the bispecific antibody group and the traditional treatment group in ORR, OS and PFS, with combined effect sizes of odds ratio (OR)=1.31 and 95% confidence interval (CI)=0.98-1.76, OR=1.36 and 95%CI=0.99-1.87 and OR=1.07 and 95%CI=0.80-1.43, respectively (p 0.07, 0.06, and 0.64, respectively). However, the incidence of irAEs was significantly lower in the bispecific antibody group (OR = 1.56; p = 0.0007), indicating a reduction in such events. Bispecific antibodies demonstrate good safety in lung cancer immunotherapy, particularly in reducing irAEs. Despite some improvements in efficacy (e.g., ORR and OS), BsAbs do not demonstrate a significant superiority over conventional treatments.

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Metaanálisis de la eficacia y la seguridad de los anticuerpos específicos en la inmunoterapia del cáncer de pulmón.

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Palabras clave: Anticuerpos Biespecíficos; Neoplasias Pulmonares; Cáncer de pulmón; Inmunoterapia; Metaanálisis; Eficacia; Seguridad.

Resumen. Este estudio tiene como objetivo evaluar sistemáticamente la eficacia y la seguridad de los anticuerpos biespecíficos en la inmunoterapia del cáncer de pulmón mediante un metaanálisis, proporcionando evidencia más completa para su aplicación clínica. Se llevó a cabo una búsqueda sistemática en PubMed, Embase, Cochrane Library y bases de datos chinas para identificar ensayos controlados aleatorizados y ensayos controlados cuasialeatorizados elegibles. Se recogieron datos clínicos sobre la terapia con anticuerpos biespecíficos para el cáncer de pulmón. Los puntos finales primarios incluyeron la tasa de respuesta objetiva (ORR), la supervivencia libre de progresión (PFS), la supervivencia general (OS) y la incidencia de eventos adversos relacionados con la inmunidad (AEIs). El análisis de datos se realizó con el software RevMan 5.3, utilizando modelos de efecto fijo o de efecto aleatorio. Se incluyeron nueve estudios, con un total de 588 pacientes. El metaanálisis no reveló diferencias estadísticamente significativas entre el grupo de anticuerpos biespecíficos y el grupo de tratamiento tradicional en ORR, OS y PFS, con tamaños de efecto combinados de OR=1.31, OR=1.36 y OR=1.07, respectivamente (valores de p de 0.07, 0.06 y 0.64, respectivamente). Sin embargo, la incidencia de AEIs fue significativamente menor en el grupo de anticuerpos biespecíficos (OR=1,56, p=0,0007), lo que indica una ventaja de estos anticuerpos en la reducción de AEIs. Los anticuerpos biespecíficos demuestran una alta seguridad en la inmunoterapia del cáncer de pulmón, en particular en la reducción de AEIs. Sin embargo, a pesar de algunas mejoras en la eficacia (tales como ORR y OS), los anticuerpos biespecíficos no muestran una superioridad significativa frente a los tratamientos convencionales.

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INTRODUCTION

In 2020, there were 2.48 million new cases of lung cancer (12.4%), making it the most prevalent cancer globally, once again surpassing breast cancer after 2020 [1-2]. The death toll reached 1.8 million (18.7%), maintaining its position as the leading cause of cancer-related deaths. Approximately 50% of global new cases and deaths from lung cancer occur in Asia [3]. In China, lung cancer remains the leading cause of cancer incidence and mortality, with an increasing trend. The main treatment options for lung cancer include surgery, chemotherapy, radiation therapy, and targeted therapy [4]. However, since most patients with lung cancer are diagnosed at an advanced stage, traditional treatments are limited in their efficacy and often come with significant side effects, which significantly impact the quality of life of patients [5].

In recent years, with the rapid development of tumour immunology, immunotherapy has become a research focus and a breakthrough direction in lung cancer treatment[6]. Immune checkpoint inhibitors (ICIs), including those targeting programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1), have achieved significant success in clinical settings, greatly extending survival in patients with lung cancer [7-8]. However, monotherapy with ICIs has notable limitations, including low efficacy, the potential for resistance, and the risk of severe immune-related adverse events (irAEs) [9]. To overcome the limitations of traditional ICI treatments, bispecific antibodies (BsAbs) have gradually attracted research attention as a novel immune therapeutic approach [10-11]. Bispecific antibodies recognise two distinct antigens or receptors simultaneously, enabling precise targeting of tumour cells while activating immune effector cells to enhance the anti-tumour immune response. Studies have shown that BsAbs can not only effectively improve the selectivity and efficacy of cancer treatments but also reduce the toxic side effects of using ICIs alone, thereby maximising the benefits of immunotherapy[10-11]. Several BsAbs have been developed and are currently being evaluated in clinical trials for the treatment of lung cancer. Among them, BsAbs targeting both PD-1/PD-L1 and other immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and lymphocyte-activation gene 3 (LAG-3), are of particular interest [6]. Preliminary results from early clinical trials suggest that these BsAbs demonstrate good anti-tumour efficacy and relatively controllable safety in patients with non-small cell lung cancer (NSCLC) [12]. However, due to significant differences in clinical trial designs, patient populations, and evaluation standards, no consistent conclusion has been reached regarding the overall efficacy and safety of bispecific antibody therapy for lung cancer. Therefore, there is an urgent need to systematically review and integrate the available clinical research data using rigorous evidence-based methods to more comprehensively and objectively evaluate the clinical value of BsAbs in lung cancer immunotherapy.

This study employs a meta-analytic approach to synthesise data from randomized controlled trials (RCTs) and clinical studies on bispecific antibody (BsAb) therapy for lung cancer, systematically evaluating its efficacy and safety to provide stronger evidence for the clinical application of BsAbs in lung cancer immunotherapy.

MATERIALS AND METHODS

Search Strategy

Relevant literature was systematically searched in multiple databases, including PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, the Wanfang Database, and the Chinese Medical Journals Database. The literature search combined subject headings (MeSH terms) and free-text terms to comprehensively identify studies that met the research criteria. The Chinese database search terms included: 'Bispecific antibody', 'Bispecific monoclonal antibody', 'Lung cancer', 'Non-small cell lung cancer', 'Small cell lung cancer', 'Immunotherapy', 'Immune checkpoint inhibitors', 'Efficacy', 'Effect', 'Safety', 'Adverse reactions' and 'Randomized controlled trials'. The specific search strategy for English databases was as follows: ('Bispecific antibody' OR 'Bispecific antibodies' OR 'Bispecific monoclonal antibody' OR 'Bispecific mAb' OR 'Dual-target antibody' OR 'BsAb') AND ('Lung cancer' OR 'Lung neoplasms' OR 'Non-small cell lung cancer' OR 'NSCLC' OR 'Small cell lung cancer' OR 'SCLC' OR 'Pulmonary carcinoma') AND ('Immunotherapy' OR 'Immune therapy' OR 'Checkpoint inhibitors' OR 'Immune checkpoint inhibitors' OR 'ICI' OR 'PD-1' OR 'PD-L1' OR 'CTLA-4' OR 'LAG-3' OR 'T cell engager') AND ('Efficacy' OR 'Effectiveness' OR 'Clinical effect' OR 'Response rate' OR 'Objective

response rate' OR 'Survival' OR 'Progression-free survival' OR 'Overall survival') AND ('Safety' OR 'Adverse events' OR 'Adverse reactions' OR 'Adverse effects' OR 'Side effects' OR 'Immune-related adverse events' OR 'irAEs') AND ('RCT' OR 'Randomized controlled trial' OR 'Clinical trial' OR 'Randomized trial').

The inclusion criteria included (1) diagnosis of NSCLC, clinical staging according to the American Joint Committee on Cancer 9th edition lung cancer staging standard (stages IIIB–IV), with negative driver gene mutation; and (2) studies with complete baseline data, with at least one measurable lesion for assessment according to the Response Evaluation Criteria in Solid Tumors (version 1.1.3); (3) study type is an RCT or quasi-randomized controlled trial (CCT), using BsAbs for lung cancer immunotherapy; and (4) the treatment group used BsAbs alone or combined with other treatments (e.g. chemotherapy, targeted therapy or other immunotherapies), and the control group received standard treatment (including placebo, chemotherapy, single immune checkpoint inhibitor therapy or other standard therapies). The **exclusion criteria** were as follows: (1) non-RCTs or studies without a clear control group; (2) multiple primary tumour sites; (3) case reports, expert opinions, literature reviews and meta-analyses; (4) studies with incomplete data or involving the inability to extract valid data; (5) repeatedly published studies or those with obvious data errors or contradictions; (6) treatment lasting fewer than two cycles; and (7) studies where informed consent from all participants was not obtained.

Outcome measures included objective response rate (ORR), categorised as complete response, partial response, stable disease, and disease progression; progression-free survival (PFS); and overall survival (OS). The primary endpoint was OS, defined as the time from receiving immunotherapy to death. The secondary endpoint was PFS, defined as the time from receiving immunotherapy to disease recurrence, progression, or death. Secondary outcomes included the incidence of adverse events (AEs) and irAEs.

Quality Assessment

Two reviewers independently searched the literature, extracted data, and assessed the methodological quality. Any disagreements were cross-checked and resolved through consensus. The quality assessment was based on the Cochrane RCT quality evaluation standards, with the quality classified as low risk, high risk, or unclear. The criteria included random allocation method, allocation concealment, blinding, completeness of outcome data, selective reporting, and other biases.

Statistical Analysis

All statistical analyses were performed using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen). Continuous variables were analysed using weighted mean difference or standardised mean difference, and binary variables using odds ratios (ORs). Results were expressed using a 95% confidence interval (CI). If studies were homogeneous ($p>0.05$; $I2 < 50\%$), a fixed-effect model was used; otherwise, a random-effects model was applied. In cases of high heterogeneity, a random-effects model was used, and publication bias was assessed using a funnel plot.

RESULTS

Literature Search and Screening Results

Through systematic searches in the PubMed, Embase, Web of Science, and Cochrane Library databases, a total of 132 potential studies were identified. Following initial screening, where duplicates were removed based on titles and abstracts, 44 studies remained. In a further screening, 26 studies were excluded due to poor quality, irrelevance to the research objectives, duplication, or low-quality or incomplete data. Finally, 9 studies were included, and data were extracted for meta-analysis. The literature screening process is shown in Fig. 1.

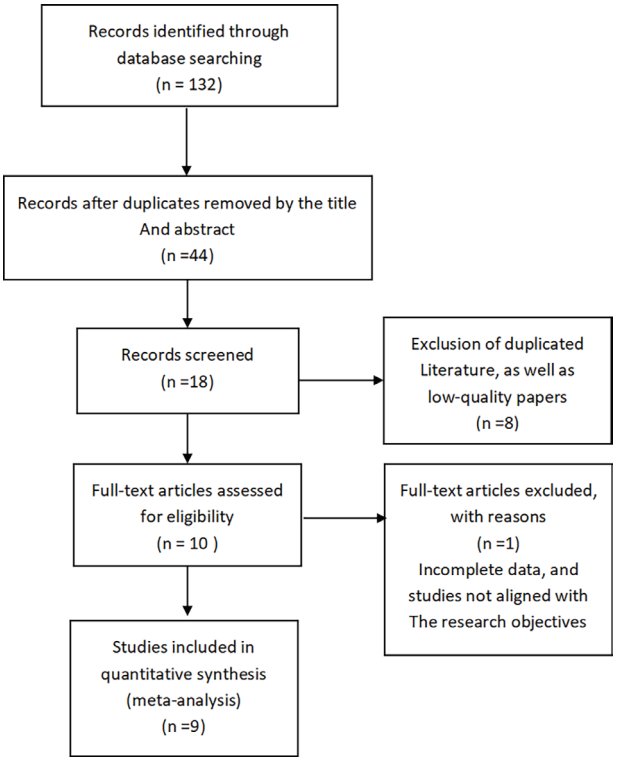

Fig. 1. Literature Screening Flowchart.

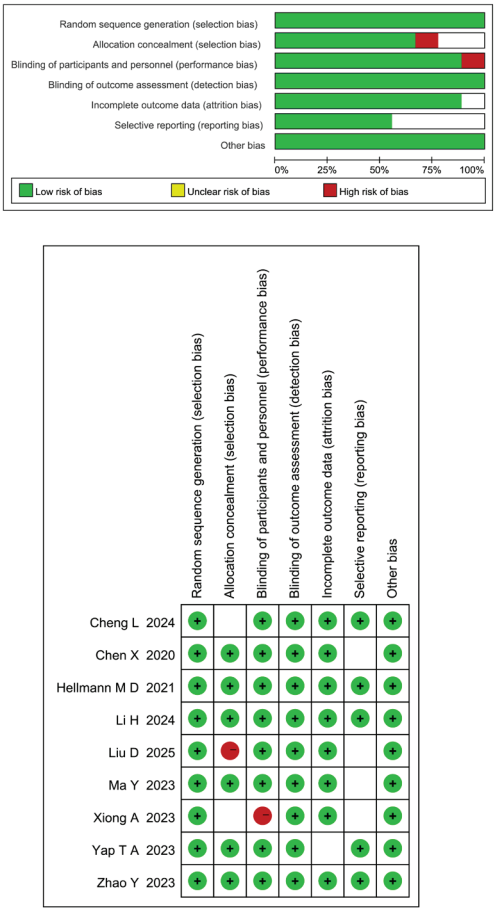

Fig. 2. Literature Quality Assessment.

Quality Assessment of Included Studies

Among the nine studies included in this research [13-21], five studies were of high methodological quality, rated as Grade A; two studies had moderate quality, rated as Grade B; and two studies were of low quality, rated as Grade C. Five studies provided detailed methods, two studies reported concealed allocation methods, and one study had comparable outcome indicators. The quality assessment is shown in Fig. 2.

Basic Characteristics of Included Studies

This analysis included nine clinical studies [13-21], with a total sample size of 588 patients. All studies were RCTs, with high quality (five rated as A). The age range of the study populations was 30–75 years, with treatment and control groups having relatively long disease durations: the treatment group had disease durations of 1-5 years, whereas the control group had durations of 1-3 years. The treatments mainly included combinations of ivosidenib with gefitinib, amivantamab, bevacizumab and other drugs, or the use of immune therapy drugs such as amivantamab, patritumab, pembrolizumab, and nivolumab alone. Treatment duration varied from 1 to 5 years. The main outcome indicators included ORR, PFS, OS, and the incidence of irAEs. All studies compared the effects of different immune therapy regimens across various disease courses and age groups, as shown in Table 1.

Objective Response Rate

This meta-analysis included nine studies comparing the ORR between two groups. All nine studies were clinical trials comparing bispecific antibody drugs with conventional drugs, with $p=0.89$ and $I^2=0\%$. The study data had homogeneity, and the com-

Table 1. Characteristics of included studies.

References	year	Sample (male/ female)	Age	Outcome	Treatment method (treatment group/ control group)	Treatment duration (years)	Disease duration (treatment group/control group)	Value of reference
Cheng L[13]	2024	53/47	60~75	①②③④	**Ivosidenib// Gefitinib, Iressa**	2	2 year/ 1 year	A
Xiong A[14]	2023	67/64	≥54	①③④	**Amivantamab/ Atezolizumab, Tecentriq**	3	2 year/ 3 year	A
Zhao Y[15]	2023	61/63	30~55	①②③	**Patritumab/ Erlotinib, Tarceva**	2	2 year/ 2 year	B
Hellmann MD[16]	2021	38/38	≥45	①②	**Amivantamab/ Nivolumab, Opdivo**	1	4 year/ 2 year	A
Liu D[17]	2025	64/64	<50	②③	**Ivosidenib// Amivantamab, Rybrevant**	2	2 year/ 2 year	C
Li H[18]	2024	43/38	≥50	①④	**Ivosidenib// Nivolumab, Opdivo**	3	1 year/ 2 year	C
Chen X[19]	2020	79/69	40~70	①②	**Patritumab Amivantamab, Rybrevant**	4	2 year/ 2 year	A
Yap TA[20]	2023	54/57	≥50	①②③④	**Ivosidenib/ Bevacizumab, Avastin**	3	5 year/ 3 year	B
Ma Y[21]	2023	34/44	≥50	①②③④	**Ivosidenib/ Pembrolizumab, Keytruda**	5	2 year/ 1 year	A

Note: ①Objective response rate (ORR); ②Progression-free survival (PFS); ③Overall survival (OS); ④Incidence of immune-related adverse events (irAEs).

bined effect size OR was calculated using a fixed-effect model, with OR=1.31 and 95% CI=0.98-1.76. There was no statistically significant difference between the two groups (p= 0.07>0.05), as shown in Fig. 3.

Overall Survival

This meta-analysis included nine studies comparing the OS between two groups. Among them, five studies compared bispecific antibody drugs with conventional drugs. With OR=1.36 and I^2=55%, the study data showed heterogeneity; therefore, the combined effect size was estimated using a random-effects model, yielding OR=1.36 (95% CI=0.99-1.87). There was no statistically significant difference between the two groups (p=0.06>0.05), as shown in Fig. 4.

Progression-Free Survival

This meta-analysis included seven studies comparing PFS between two groups. All seven studies were clinical trials evaluating bispecific antibody drugs against conventional drugs. With p=0.02 and I^2=61%, the data showed heterogeneity, and the combined effect size OR was calculated using a random-effects model, resulting in OR=1.07 and 95% CI=0.80-1.43. There was no statistically significant difference between the two groups (p=0.64 > 0.05), as shown in Fig. 5.

Adverse Event Incidence

This meta-analysis included six studies comparing the incidence of AEs between two groups. All six studies were clinical trials comparing bispecific antibody drugs with conventional drugs. With p=0.31 and I^2=16%, there was no heterogeneity in the study data, and the combined effect size OR was calculated using a fixed-effect model, with OR=1.68 and 95%CI=1.12-2.54. There was a statistically significant difference between the two groups in the incidence of AEs (p=0.01; <0.05), as shown in Fig. 6.

Immune-Related Adverse Event Incidence

This meta-analysis included six studies comparing irAEs between two groups. All six were clinical trials comparing bispecific antibody drugs with conventional drugs. With p=0.17 and I^2=35%, there was no heterogeneity in the data, and the combined effect size OR was calculated using a fixed-effect model, with OR=1.56 and 95% CI=1.13-2.16. A statistically significant difference was observed between the two groups in the incidence of immune-related adverse events (p=0.0007; <0.05), as shown in Fig. 7.

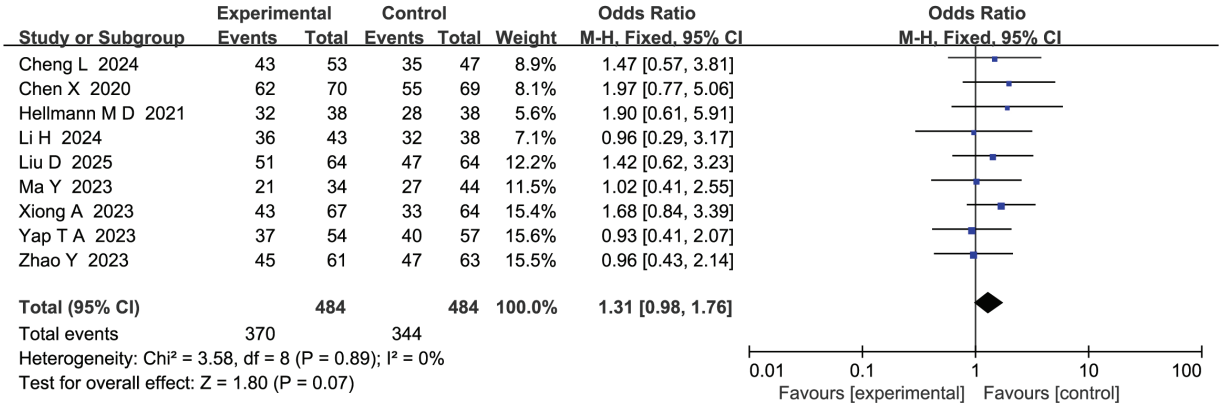

Fig. 3. Forest plot Analysis of Objective Response Rate (ORR) for Bispecific Antibodies in Lung Cancer Immunotherapy.

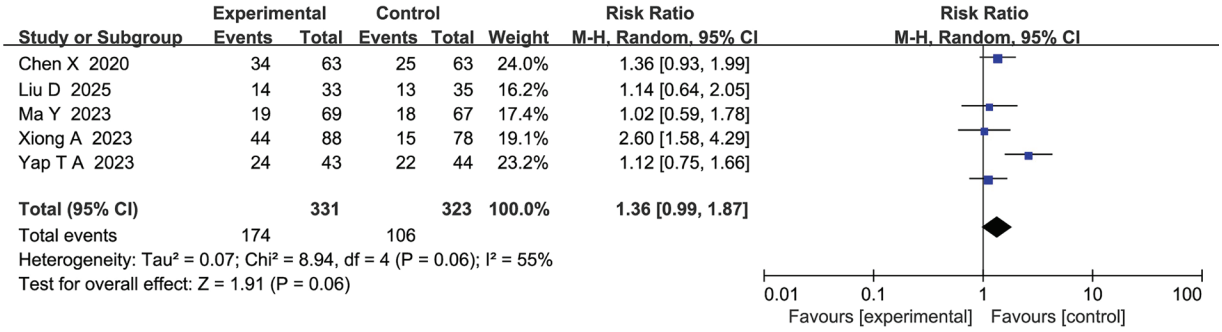

Fig. 4. Forest plot Analysis of Overall Survival (OS) for Bispecific Antibodies in Lung Cancer Immunotherapy.

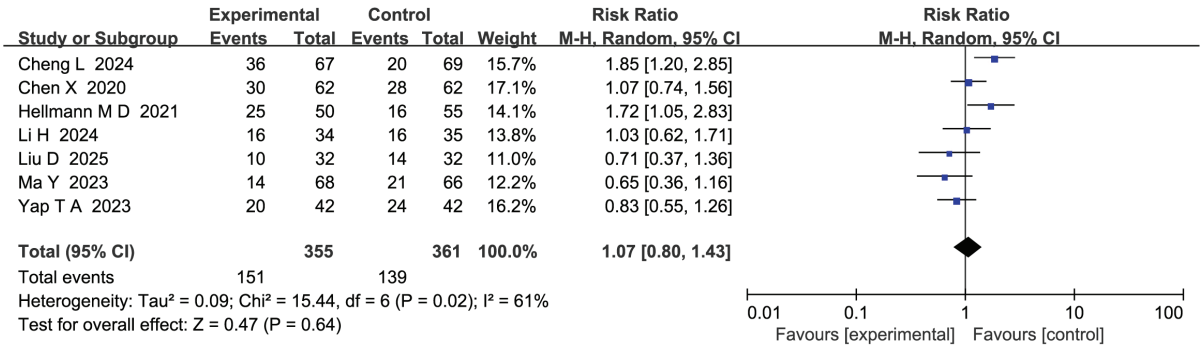

Fig. 5. Forest plot Analysis of Progression-Free Survival (PFS) for Bispecific Antibodies in Lung Cancer Immunotherapy.

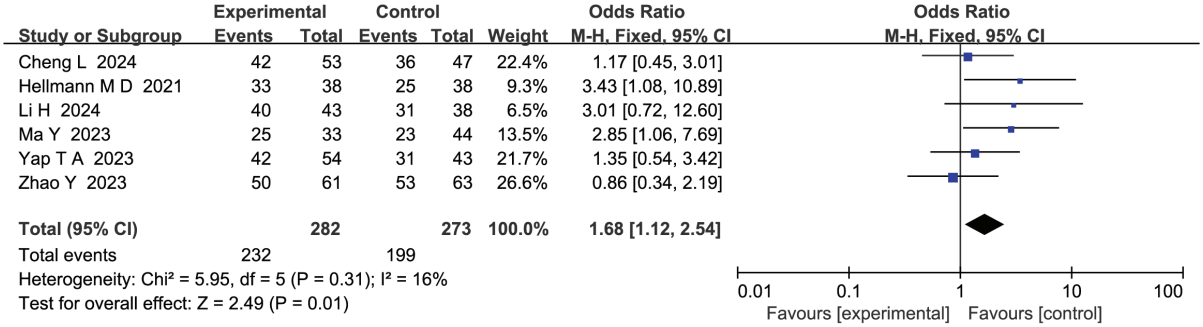

Fig. 6. Forest plot Analysis of Adverse Events (AEs) Incidence for Bispecific Antibodies in Lung Cancer Immunotherapy.

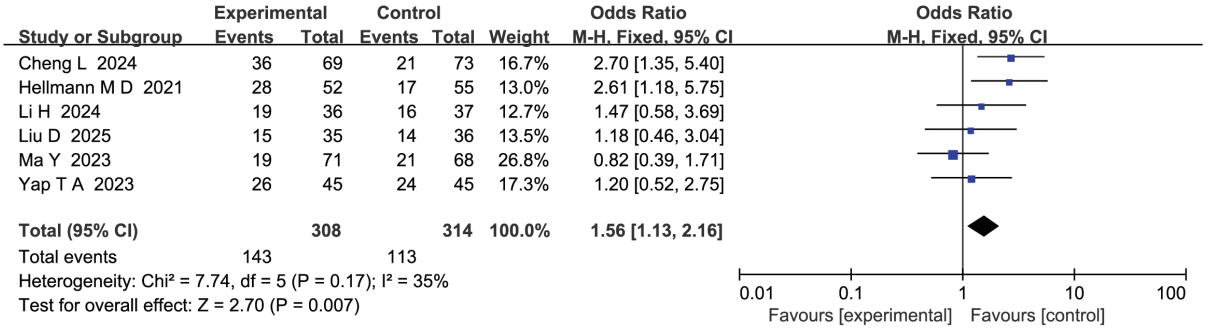

Fig. 7. Forest plot Analysis of Immune-Related Adverse Events (irAEs) Incidence for Bispecific Antibodies in Lung Cancer Immunotherapy.

Publication Bias Assessment

The results of the publication bias assessment for the efficacy and safety of bispecific antibody drugs in lung cancer immunotherapy are displayed in Fig. 8. The studies included were symmetrically spread out in the funnel plot, indicating little publication bias. Most of the scatter points were clustered in the upper part of the funnel plot, implying that the samples in the studies were representative and highly accurate.

DISCUSSION

As the leading cause of cancer-related death worldwide, lung cancer has experienced a steady increase in cases in recent years, particularly in Asia, where it has be-

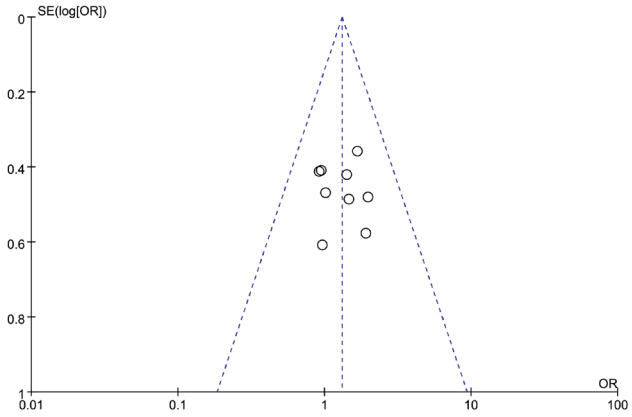

Fig. 8. Funnel plot of Meta-Analysis on the Efficacy and Safety of Bispecific Antibodies in Lung Cancer Immunotherapy.

come the most common type of cancer [22-23]. The treatment approach for lung cancer has gradually shifted from early-stage surgery, chemotherapy, and radiotherapy to targeted therapy and immunotherapy [24]. This meta-analysis indicates that BsAbs may have potential in the efficacy and safety of lung cancer immunotherapy. Although there was no significant difference between the bispecific antibody group and the conventional treatment group in ORR or OS, BsAbs showed an advantage in lowering irAEs.

In this meta-analysis, the bispecific antibody group did not show a significant difference in ORR compared to the conventional treatment group (OR = 1.31; p = 0.07). This result offers initial insight into the potential of BsAbs in lung cancer treatment. Previous studies have demonstrated that BsAbs enhance anti-tumor immune responses through two mechanisms [25]. Although no significant difference in ORR was observed between the bispecific antibody and conventional treatment groups in the overall population, some patients may benefit more from BsAbs. Certain studies have found that, in specific lung cancer patients, combinations of BsAbs exhibit significant synergistic effects [26]. This research indicates that, although the overall ORR in some clinical trials has not shown substantial improvement, BsAbs might be more effective in particular tumor immune phenotypes [27]. The study highlights that small sample sizes can reduce the statistical significance of clinical outcomes, especially in early clinical stages. Therefore, larger-scale clinical trials are needed to provide more definitive evidence.

Regarding OS, the results of this study indicated no statistically significant difference between the bispecific antibody and conventional treatment groups (OR=1.36, p=0.06), although a trend toward effect was observed. This conclusion suggests that BsAbs may not significantly extend patient survival or, at least, no definitive conclusion can be drawn from the current data. Furthermore, with respect to PFS, the study's results showed no significant difference (OR=1.07, p=0.64). This phenomenon may be related to the mechanism of action of BsAbs. Many early clinical trials have indicated that although BsAbs can improve immune responses, their effects often take longer to manifest because of their mechanism of enhancing T-cell-mediated immunity [28]. Therefore, the heterogeneity in this study (I2=55%) may also have contributed to inconsistent PFS results. When BsAbs are combined with other immunotherapies, heterogeneity in efficacy may arise due to differences in combination regimens, dosages, and individual patient characteristics [29]. In the analysis of irAEs, the incidence in the bispecific antibody group was significantly lower than that in the conventional treatment group (OR=1.56, p=0.0007). This result indicates that BsAbs have certain advantages in reducing irAEs. Immune-related adverse events are one of the most significant side effects of traditional immunotherapies, with common adverse effects including rashes, colitis, and immune damage to other organs [30]. However, due to their targeted properties, BsAbs can activate the immune system more precisely, thereby reducing damage to non-target tissues and lowering the occurrence of adverse effects[31]. According to other studies, as a bispecific antibody, amivantamab has shown a lower

incidence of immune-related side effects in clinical studies, which is closely related to its dual-targeting mechanism [22]. By targeting both EGFR and PD-L1, amivantamab can enhance immune responses while reducing attacks on normal tissues, thereby decreasing the occurrence of irAEs [32].

Recently, numerous dual-antibody drugs have been tested in clinical trials and approved for use. First, phase III data published in 2025 (NCT05184795) showed that in patients with EGFR-TKI-resistant NSCLC, ivonescimab (AK112, a PD-1/VEGF dual antibody) combined with chemotherapy significantly prolonged median (m)PFS compared to chemotherapy alone (mPFS: 7.4 months vs. 4.8 months, hazard ratio: 0.55, $p<0.001$), and the incidence of ≥grade 3 irAEs was only 6.8%, which was significantly lower than the historical data of traditional immune combination regimens (approximately 15%). This result suggests that a dual pathway blockade strategy (immunization + anti-angiogenesis) can further reduce the burden of irAEs while improving efficacy, consistent with the present study's conclusion that BsAbs may reduce irAEs, albeit with a greater magnitude of effect [33, 34].

Second, in the DeLLphi-301 study published in 2024, tarlatamab (AMG 757, DLL3×CD3 double antibody) achieved an ORR of 41% with manageable safety, including a cytokine release syndrome ≥ grade 3 incidence of 3% in patients with relapsed small cell lung cancer (SCLC). Although SCLC is not the focus of this study, the success of tarlatamab shows that double antibodies have a comparable breakthrough potential in immune 'cold' tumors, providing new evidence for future meta-analyses that include a broader range of lung cancer subtypes [35].

However, this study has some limitations. In this meta-analysis, heterogeneity among studies may influence how applicable the results are. The sources of heterogeneity can vary, including differences in study design, treatment protocols, and patient groups. For instance, the studies included in this review used different treatment protocols, such as single BsAbs, combined with chemotherapy, or used alongside other immunotherapies. These protocols may have different effects depending on the patient populations. Many studies have pointed out that variations in treatment protocols are a key factor affecting the outcomes of meta-analyses. Treatment length, drug doses, and patient immune status can all impact the overall effectiveness and safety. Therefore, future research should focus on standardizing treatment protocols, increasing sample sizes, and performing more detailed stratified analyses of patient groups to reduce the influence of heterogeneity on the results.

CONCLUSION

Overall, BsAbs show promise in lung cancer immunotherapy, especially in reducing irAEs. However, regarding effectiveness in ORR, OS, and PFS, their impact does not significantly differ from traditional immunotherapy. This may be due to the mechanism of action of BsAbs, the variety of treatment regimens, and the heterogeneity among patient populations.

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Competing interest

The authors declare that they have no competing interests.

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Author contributions

Study conception and design: XZ, YL; data collection: XZ, YL; data analysis and interpretation: XZ, YL; drafting of the article: XZ, YL. Critical revision of the article: XZ, YL.

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