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Review Article

Efficacy and safety of pembrolizumab in the treatment of advanced non-small cell lung cancer: a systematic review and meta-analysis

Kaiheng Gao[1*], Nadier Yimin[2*], Binbin Song[3,4], Hong Pan[3,4], Zhouyi Lu[1]

[1]Department of Cardiothoracic Surgery, Huashan Hospital Affiliated to Fudan University, Jing'an District, Shanghai 200040, China; [2]Department of Anesthesiology, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, China; [3]Department of Oncology, Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan, China; [4]Department of Oncology, Chinese People's Liberation Army Western Theater General Hospital, Chengdu 610083, Sichuan, China. [*]Co-first authors.

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Abstract: Background: Advanced non-small cell lung cancer (NSCLC) remains a challenging condition with limited treatment options. Pembrolizumab, a programmed death-1 (PD-1) inhibitor, has emerged as a promising therapy, necessitating a comprehensive analysis of its efficacy and safety. Methods: Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a thorough search across major electronic databases to compile studies evaluating Pembrolizumab's efficacy and safety in treating advanced NSCLC. Thirteen studies were included based on stringent inclusion and exclusion criteria, focusing on the objective response rate (ORR), disease control rate (DCR), and adverse event incidence. Statistical analyses assessed study heterogeneity and effect sizes, employing fixed or random-effects models as appropriate. Results: The meta-analysis revealed an ORR of 0.46 (95% CI: 0.44-0.49) and a DCR of 0.74 (95% CI: 0.69-0.79), indicating significant tumor control and disease management. Sensitivity analyses confirmed the robustness of these findings. The overall incidence of adverse events was reported as 36% (95% CI: 32% to 40%), reflecting a manageable safety profile. Publication bias evaluation showed no significant bias, affirming the reliability of the results. Conclusions: Pembrolizumab exhibits substantial efficacy in reducing tumor burden and controlling disease in patients with advanced NSCLC, alongside a consistent safety profile. These findings support its continued use and further research into optimizing treatment strategies.

Keywords: Pembrolizumab, non-small cell lung cancer, meta-analysis, objective response rate, disease control rate

Introduction

Lung cancer is the predominant cause of cancer-related deaths globally, with non-small cell lung cancer (NSCLC) constituting around 85% of all instances [1]. The therapy of advanced NSCLC has dramatically transformed during the past two decades, with the emergence of targeted treatment and immunotherapy heralding a new era in treatment paradigms [2, 3]. Pembrolizumab, a highly selective humanized monoclonal antibody targeting programmed death 1 (PD-1), has become a fundamental component in the treatment of advanced NSCLC owing to its ability to augment the immune response against tumor cells [4, 5].

Historically, the prognosis for advanced NSCLC has been unfavorable, with restricted treatment alternatives predominantly centered on chemotherapy, which provides minimal survival advantage and is sometimes linked to considerable toxicity [5]. The identification of molecular changes that promote tumor growth resulted in the creation of tailored medicines, enhancing results for a specific group of patients. Nonetheless, the sustainability of response persisted as a concern, and not all patients qualify for these targeted therapies [6]. The emergence of immunotherapy, especially immune checkpoint inhibitors such as pembrolizumab, has transformed the treatment of NSCLC by providing sustained responses and the possibility of pro-

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longed survival in certain patients [7]. Pembrolizumab functions by inhibiting the PD-1 receptor, a critical immunological checkpoint that, once activated, reduces T-cell immune responses against neoplastic cells [8]. Pembrolizumab enhances antitumor immunity by blocking this mechanism, resulting in the possibility of strong and enduring responses [9]. The efficacy and safety profile has been assessed in multiple pivotal clinical trials, which have broadened its indications and defined its use in numerous contexts, including as a first-line treatment and in conjunction with other therapeutic agents [10].

Notwithstanding the advantages of pembrolizumab, its administration has certain risks. Immune-related adverse events (irAEs), resulting from immune system activation, can afffect several organ systems and exhibit considerable variability in severity [11]. Effective management of these irAEs is essential for preserving quality of life and facilitating ongoing therapy [12]. This systematic review and meta-analysis intend to thoroughly evaluate the current data regarding the efficacy and safety of pembrolizumab for treating patients with advanced NSCLC. By aggregating data from randomized controlled trials and observational studies, we aim to deliver a comprehensive synthesis of evidence to direct clinical practice, inform subsequent research, and ultimately enhance patient outcome.

Materials and methods

Search strategy

During our systematic review and meta-analysis, we meticulously followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria to uphold rigorous standards of research and reporting [13]. PRISMA's help was essential in formulating our research strategy and presentation, including a 27-item checklist and a systematic approach to guarantee the thoroughness and transparency of our review.

On November 16, 2023, we executed a comprehensive search across four principal electronic databases: PubMed, Embase, Web of Science, and Cochrane Library, without temporal constraints to encompass the entirety of published literature. Our search strategy was carefully constructed around key phrases important to our PICO framework: "advanced non-small cell lung cancer", "pembrolizumab", "immunotherapy", "efficacy", "safety", "survival rate", "tumor response", and "adverse events". This selection was designed to provide extensive yet important coverage of the topic, enabling a thorough retrieval of research related to the efficacy and safety of pembrolizumab in the treatment of advanced NSCLC. We did not limit our search to a certain language, therefore broadening our access to international research results. Additionally, we meticulously examined the reference lists of the selected papers to guarantee that no major study was omitted.

Inclusion criteria and exclusion criteria

Inclusion criteria: 1. Study Design: Included studies were randomized controlled trials (RCTs), cohort studies, or case-control studies that reported on the efficacy and/or safety of pembrolizumab in treating advanced NSCLC. 2. Population: Studies involving patients diagnosed with advanced non-small cell lung cancer were included. We defined advanced NSCLC as stages IIIA, IIIB, and IV according to the American Joint Committee on Cancer (AJCC) staging system. 3. Intervention: The primary intervention of interest was treatment with pembrolizumab. Studies were included if pembrolizumab was administered alone or in combination with other therapies as part of the treatment regimen. 4. Outcomes: Studies must have reported on at least one of the following outcomes: overall survival, progression-free survival, response rate, or safety profile, including the incidence and type of adverse events. 5. Language and Publication Status: There were no restrictions on language or publication status; both published and unpublished studies were considered to minimize publication bias.

Exclusion criteria: 1. Non-Relevant Study Designs: Editorials, letters, reviews, animal studies, and phase I trials focusing solely on pharmacokinetics or dose-finding were excluded. 2. Non-Eligible Population: Studies focusing on patients with non-advanced stages of NSCLC or other types of cancers were excluded. 3. Non-Pembrolizumab Treatments: Studies that did not specifically investigate pembrolizumab or its combination as a therapeutic intervention

were excluded. 4. Insufficient Data: Studies without clear outcome measures related to efficacy or safety, or those lacking sufficient data for extraction and analysis were excluded. 5. Duplicate Data: Studies reporting duplicate or overlapping data were excluded to avoid double-counting.

Data extraction

We adopted a methodical strategy for data extraction to guarantee precision and comprehensiveness. Two separate evaluators conducted the literature screening and data extraction process, each analyzing the research to extract pertinent data. They subsequently verified their findings to guarantee consistency and reliability. In case of disagreement, the evaluators convened to resolve discrepancies, and if consensus was unattainable, a third-party reviewer was engaged for an impartial resolution. The extracted data from each study comprised the author(s) names, publication year, and the number of cases analyzed. Furthermore, outcome measurements and clinical baseline data, including smoking history, gender, and age, were gathered. In instances where relevant data were absent from published papers, we reached out to the original investigators by email to solicit any unpublished data, so striving to mitigate information bias and guarantee a thorough data set for our study.

Quality assessment

Two independent evaluators assessed the quality of the included papers in our meta-analysis using the Newcastle-Ottawa Scale (NOS) [14]. This scale, an established research instrument, allocates nine points across three domains: selection, comparability, and outcome, to detect potential biases. Within the NOS framework, points are denoted by asterisks, each contributing to the total quality score of the study, which spans from 0 to 9. Following the evaluation, studies were classified according to their scores: 0-3 points indicated low quality, 4-6 points identified moderate quality, and 7-9 points signified excellent quality, facilitating a systematic and thorough quality assessment.

Statistical analyses

In our meta-analysis, a series of statistical methods were employed to synthesize data, assess heterogeneity, evaluate robustness, and identify potential publication bias: Heterogeneity across studies was evaluated using Cochran's Q test (chi-square test) to detect variability and quantified by the I^2 statistic. An I^2 value < 50% combined with a *P*-value ≥ 0.10 indicated low heterogeneity, for which a fixed-effect model was applied. Conversely, an $I^2 \geq 50\%$ or a *P*-value < 0.10 suggested substantial heterogeneity, necessitating the use of a random-effects model (DerSimonian and Laird method). For binary outcomes (e.g., ORR, DCR, and adverse event rates), pooled effect sizes were calculated using proportions, expressed as risk estimates with 95% confidence intervals (CIs). Both fixed-effect and random-effects models were applied based on the level of heterogeneity. Sensitivity analyses were performed to assess the stability of the pooled estimates by sequentially excluding individual studies and recalculating the overall effect size. This method allowed the evaluation of potential outlier effects or study-level biases. Publication bias was assessed through visual inspection of funnel plot symmetry. Egger's linear regression test was used as a quantitative measure to evaluate small-study effects, with a *P*-value < 0.05 indicating potential publication bias. Adverse event rates were analyzed using pooled proportions derived from studies reporting relevant safety outcomes. Homogeneity was confirmed with I^2 statistics, and results were synthesized using a fixed-effect model when heterogeneity was low. All analyses were conducted using Stata version 17. Two-sided *P*-values < 0.05 were considered significant. CIs were set at 95% to reflect the precision of estimates.

Results

Search results and study selection

During the preliminary phase of our systematic review and meta-analysis, an exhaustive search produced 1699 possibly pertinent papers. The further elimination of duplicates yielded a refined compilation of distinct studies. Titles and abstracts were meticulously evaluated according to established inclusion and exclusion criteria, taking into account study methodology, population demographics, measured results, and research quality. This resulted in the selection of 49 articles for comprehensive full-text examination. Independent assessments by

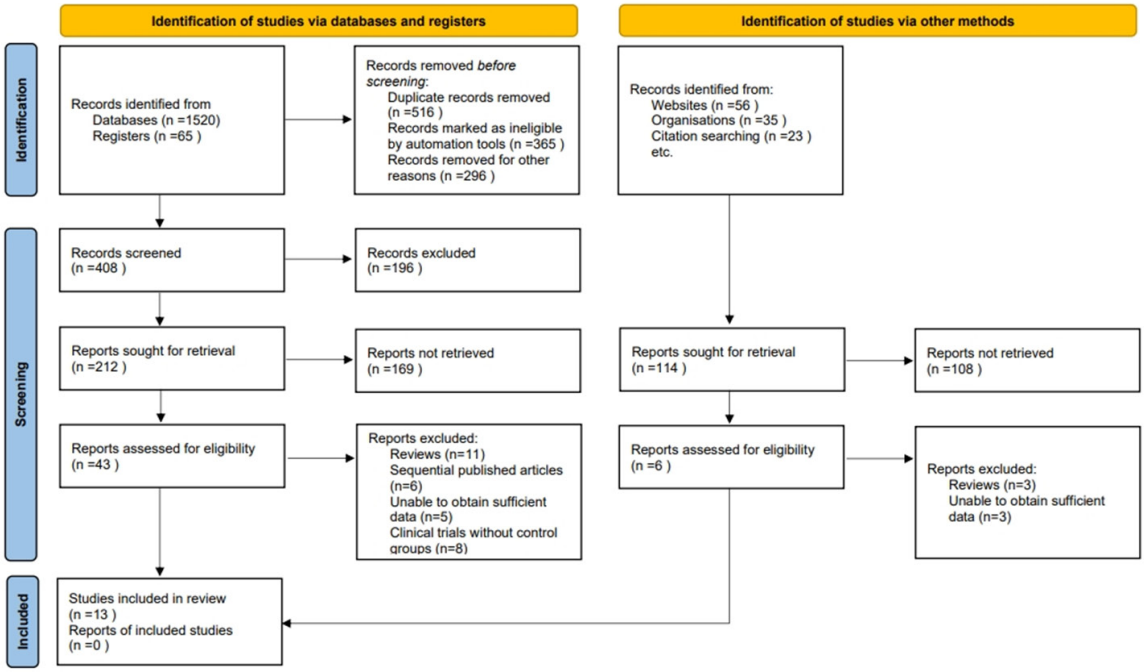

Figure 1. Study inclusion flow diagram.

several researchers further refined the selection. Thirty-six papers were removed due to specific exclusion criteria, comprising 14 review articles, 6 consecutively published studies, 8 with inadequate data, and 8 without control groups in clinical trials. Ultimately, 13 studies met all rigorous selection criteria and were incorporated into the final meta-analysis [15-27] (**Figure 1**).

Study characteristics of pembrolizumab treatment

This meta-analysis aggregates data from multiple studies examining the treatment of advanced non-small cell lung cancer with Pembrolizumab. The research covered, primarily carried out in multicenter environments, was published between 2018 and 2020. Sample sizes range from 17 participants in the smallest research to 899 participants in the largest. Treatment regimens predominantly involve Pembrolizumab administration, with some documented variations in dosage and frequency, including 120 mg every three weeks or 200 mg every three weeks. The duration of treatment and median follow-up times differed among trials, with some failing to publish these measures. The bulk of these studies lacked particular information regarding dosage, frequency, and therapy duration, indicating a variety of methodologies in clinical environments (**Table 1**).

Results of quality assessment

In our meta-analysis, we evaluated the quality of each included cohort research utilizing the Newcastle-Ottawa Scale. The studies often exhibited high quality, with scores between 7 and 9 out of a maximum of 9 points. Critical aspects, including the representativeness of the exposed cohort, selection of the non-exposed cohort, determination of exposure, and comparability of cohorts based on design or analysis, were consistently well-managed in the majority of studies. The evaluation of outcomes and the sufficiency of follow-up were generally comprehensive, enhancing the reliability of the findings. Although certain studies revealed potential for enhancement in some respects, the aggregate quality of the included research was sufficient and valid to synthesize the existing information about the efficiency and safety of Pembrolizumab in the treatment of advanced non-small cell lung cancer (**Table 2**).

Table 1. Characteristics of studies on pembrolizumab treatment

First Author	Year	Sample Size (n)	Treatment	Center Type	Dosage & Frequency	Median Follow-Up (Months)	Treatment Duration (Months)
Cortellini [23]	2020	899	Pembrolizumab	Multicenter	NA	14.6	NA
Ksienski [20]	2019	190	Pembrolizumab	Multicenter	120 mg, q3w	NA	4.9
Aguilar [16]	2019	187	Pembrolizumab	Multicenter	NA	12.6	4.53
Metro [21]	2020	282	Pembrolizumab	Multicenter	200 mg, q3w	8.7	NA
Imai [17]	2019	128	Pembrolizumab	Multicenter	NA	NA	5.6
Alessi [26]	2020	234	Pembrolizumab	Multicenter	NA	14.8	> 0.68
Amrane [18]	2019	108	Pembrolizumab	Multicenter	NA	8.2	7.3
Wakuda [22]	2020	87	Pembrolizumab	Single Center	NA	18	> 1.5
Tamiya [27]	2019	213	Pembrolizumab	Multicenter	200 mg, q3w	11	NA
Afzal [15]	2018	17	Pembrolizumab+Chemotherapy	Single Center	NA	4.99	2.56
Edahiro [19]	2019	149	Pembrolizumab	Multicenter	NA	12	NA
Sakai [24]	2020	52	Pembrolizumab	Single Center	NA	16.7	NA
Tambo [25]	2020	95	Pembrolizumab	Multicenter	NA	8.8	NA

Notes: NSCLC = Non-Small Cell Lung Cancer; NA = Not Available; q3w = Every 3 weeks; Chemotherapy = Combination treatment with chemotherapy drugs.

Table 2. Quality assessment according to Newcastle-Ottawa Scale (NOS)

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome Of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough	Adequacy of follow up of cohorts	Total score
Cortellini [23]		★	★	★	★★	★	★	★	8
Ksienski [20]	★	★	★	★	★★	★	★	★	9
Aguilar [16]	★	★	★	★	★★	★	★	★	9
Metro [21]	★	★		★	★	★	★	★	7
Imai [17]	★	★		★	★	★	★	★	7
Alessi [26]	★	★	★	★	★★	★	★	★	9
Amrane [18]	★	★		★	★	★	★	★	7
Wakuda [22]	★		★	★	★	★	★	★	7
Tamiya [27]	★	★	★	★	★	★	★	★	8
Afzal [15]	★	★	★	★	★★	★	★	★	9
Edahiro [19]		★	★	★	★★	★	★	★	8
Sakai [24]	★	★	★	★	★★	★		★	8
Tambo [25]	★	★	★	★	★★	★	★	★	9

★: one point.

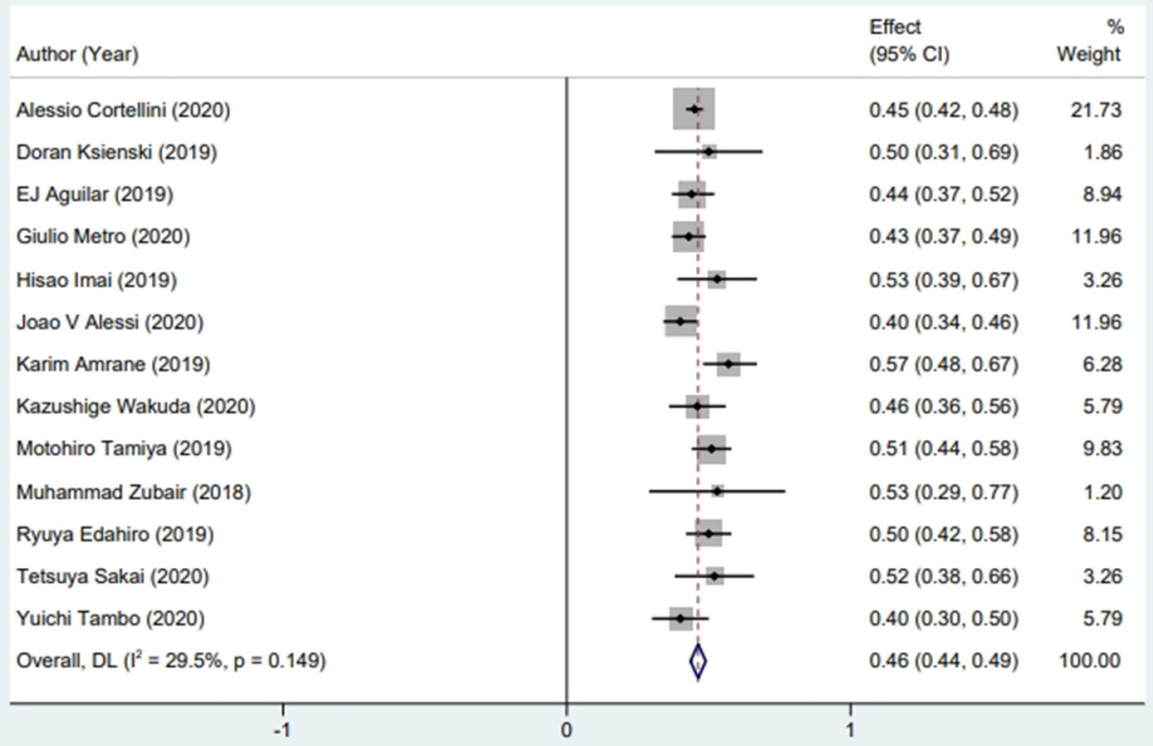

Figure 2. Forest plot depicting Objective Response Rate (ORR) of pembrolizumab in advanced Non-Small Cell Lung Cancer (NSCLC).

Meta-analytical assessment of pembrolizumab's objective response rate in advanced non-small cell lung cancer treatment

The objective response rate (ORR) was assessed in our meta-analysis across thirteen studies involving patients administered Pembrolizumab. A statistical synthesis of these research was performed to ascertain the aggregate ORR. The analysis demonstrated an absence of statistical heterogeneity across the included studies (P = 0.149, I^2 = 29.5%), signifying a uniform effect across studies and permitting the application of a fixed-effect model for the aggregated analysis. The aggregated findings from the fixed-effect model indicated that the overall ORR for the Pembrolizumab therapy cohort was 0.46 (95% CI: 0.44-0.49, **Figure 2**). This signifies that about fifty percent of the patients had either a partial or complete response to Pembrolizumab.

Meta-analysis of disease control rate for pembrolizumab in advanced non-small cell lung cancer

This meta-analysis included eight studies to assess the disease control rate (DCR) of Pembrolizumab in treating advanced NSCLC. The meta-analysis of the studies' DCR revealed statistical heterogeneity (P = 0.012, I^2 = 61.0%), requiring the use of a random-effects model for data synthesis. The application of the random-effects model recognizes the heterogeneity in study outcomes, which may stem from disparities in study design, patient demographics, or treatment protocols. The combined results indicate a significant DCR of 0.74 (95% CI: 0.69-0.79) for individuals treated with Pembrolizumab, as illustrated in **Figure 3**. This consolidated DCR indicates a substantial percentage of the trial group attaining stable disease, partial response, or complete response, highlighting Pembrolizumab's efficacy in treating advanced NSCLC. The detected heterogeneity necessitates additional study to ascertain key elements and comprehend their influence on treatment outcome. Sensitivity studies may clarify the sources of variation and aid in customizing Pembrolizumab medication to improve patient outcomes in clinical practice.

Sensitivity analysis of pembrolizumab's disease control rate in advanced non-small cell lung cancer

A sensitivity analysis was essential because of the considerable heterogeneity in the initial

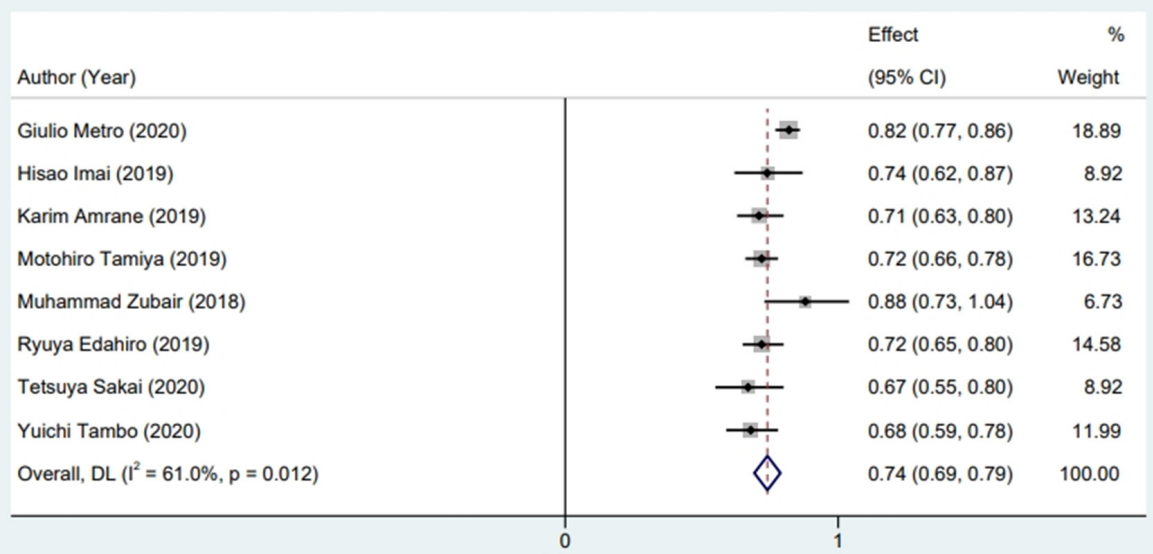

Figure 3. Forest plot illustrating Disease Control Rate (DCR) of pembrolizumab in advanced Non-Small Cell Lung Cancer (NSCLC).

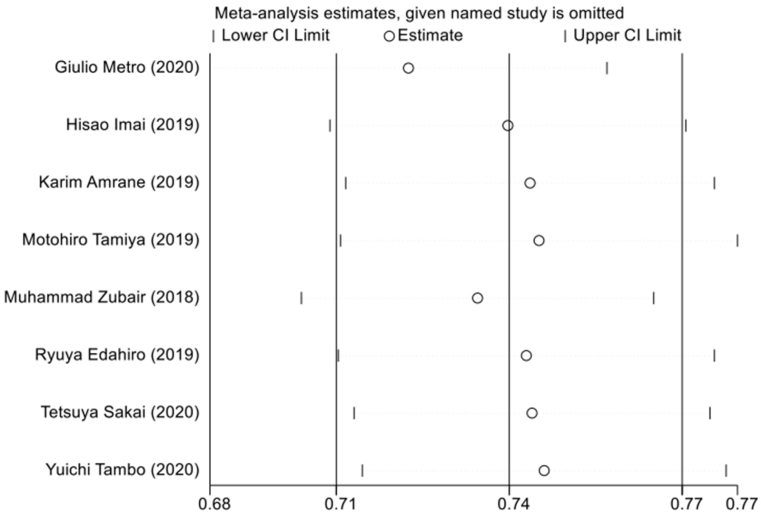

Figure 4. Sensitivity analysis graph for Disease Control Rate (DCR) in advanced Non-Small Cell Lung Cancer (NSCLC) Treated with Pembrolizumab.

meta-analytic assessment of Pembrolizumab's cancer control rate. To assess the robustness of cancer control rate obtained from the combined data, we systematically excluded each research sequentially and recalculated the overall effect size. The results of this thorough approach validated the stability of the disease control rate, indicating that the overall estimate was not unduly influenced by any individual study. The stability of the impact magnitude, despite the exclusion of individual studies, reinforces the reliability of the meta-analytical findings. This strategy enhances the trustworthiness of the evidence, indicating a genuine effect of the intervention across various research contexts (**Figure 4**).

Meta-analytical evaluation of adverse event incidence with pembrolizumab therapy

This meta-analysis evaluated six trials to assess the incidence of adverse events linked to Pembrolizumab in the treatment of diverse diseases. A synthesis of these trials indicated adverse event rates, showing no substantial statistical heterogeneity (P = 0.158, I^2 = 33.2%). The uniformity enabled the use of a fixed-effect model to consolidate the findings. The comprehensive analysis employing the fixed-effect model revealed that the total incidence of adverse events in patients receiving Pembrolizumab medication was 36% (95% CI: 32% to 40%), as illustrated in **Figure 5**. This range signifies a significant yet stable safety profile across the included studies.

Assessment of publication bias

A publication bias assessment was performed in our meta-analysis to guarantee the validity of the findings. Funnel plots, which visually depict

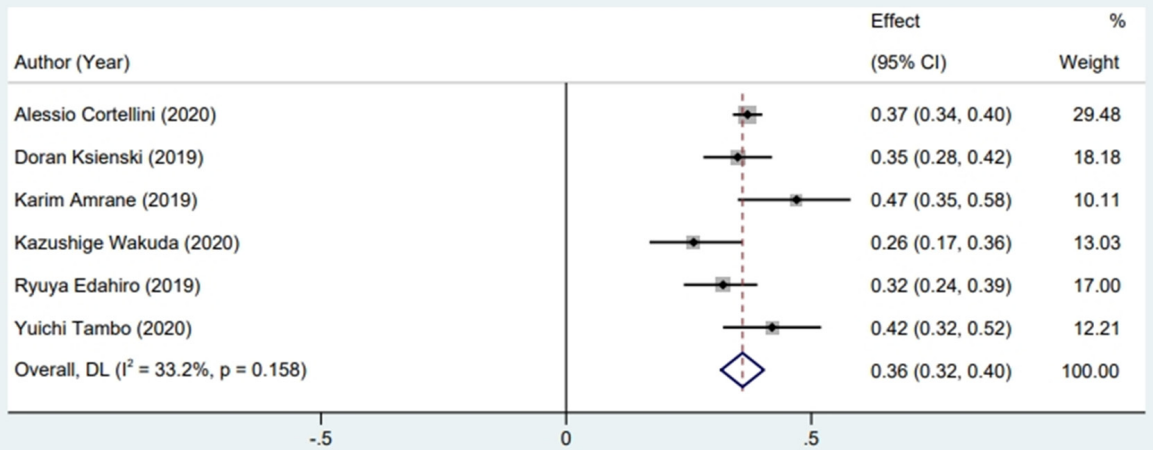

Figure 5. Forest plot showing incidence of Adverse Events (AEs) in pembrolizumab treatment.

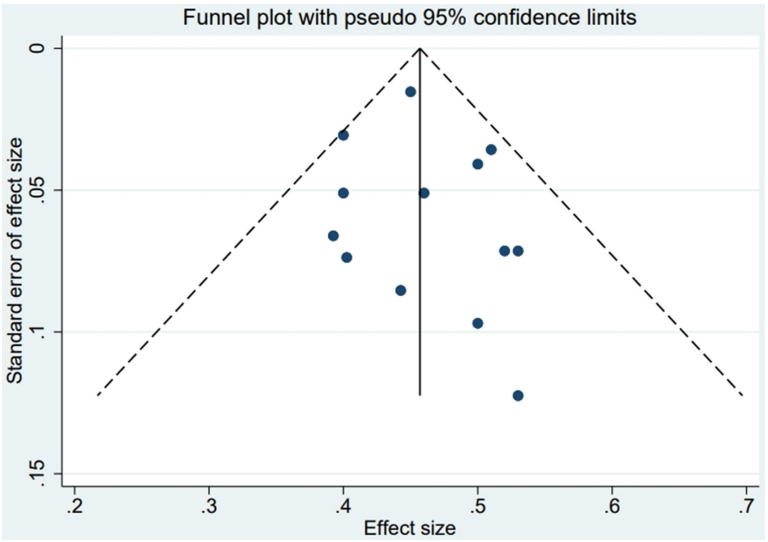

Figure 6. Funnel plot analysis for assessing publication bias in the meta-analysis.

the correlation between study size and effect size, were employed for the included research. The symmetry evident in these plots indicates a lack of publishing bias, as asymmetry in a funnel plot frequently signifies such bias (**Figure 6**).

Discussion

The advancement and approval of immunotherapeutic drugs, particularly Pembrolizumab, represent a pivotal achievement in the treatment of advanced NSCLC, which has historically been characterized by poor prognosis and restricted efficacy of standard therapy [28]. Pembrolizumab, a PD-1 inhibitor, functions by revitalizing the immune system to identify and attack cancer cells, signifying a transition from directly targeting tumors to enhancing the patient's immunological response [29]. The efficacy and safety profile of Pembrolizumab, evidenced by numerous clinical trials and real-world investigations, has resulted in its acceptance as a standard treatment in diverse clinical contexts of NSCLC. Our meta-analysis, synthesizing data from many studies, highlights the substantial objective response and disease control rates linked to Pembrolizumab, indicating its strong anti-tumor efficacy [30]. Furthermore, the safety profile identified in the meta-analysis, despite a significant occurrence of adverse events, corresponds to the established side effects of immunotherapies, which are typically more tolerable and less harmful to quality of life than conventional chemotherapy [31].

The ORR functions as an immediate metric of tumor decrease following treatment, offering an early assessment of therapeutic efficacy. This meta-analysis reveals a pooled ORR of 0.46 from thirteen studies, indicating significant tumor reduction in almost fifty percent of patients administered Pembrolizumab. This

discovery is notable for advanced NSCLC, a condition frequently linked to unfavorable prognosis with few therapeutic alternatives. The minimal heterogeneity indicates a uniform therapeutic effect of Pembrolizumab across several investigations, underscoring its efficacy as a valuable therapy option in multiple clinical contexts and patient populations. The influence of an ORR of this magnitude transcends basic statistical significance; it signifies substantial therapeutic consequences. A significant decrease in tumor size may result in symptom alleviation, enhanced physical function, and maybe extended survival, thus improving the overall quality of life for patients. Moreover, in comparison to the historical effectiveness of conventional chemotherapy, Pembrolizumab's advantageous profile highlights advancement in NSCLC treatment and provides renewed optimism for both patients and clinicians.

Disease control rate (DCR) is a comprehensive metric of treatment efficacy, including both individuals who have tumor reduction and those whose condition has stabilized. A high DCR signifies the drug's capacity to both reduce tumor size and impede disease progression. Our meta-analysis indicated a DCR of 0.74, signifying that a substantial majority of patients either exhibited tumor shrinkage or sustained stable illness. This is especially significant in advanced NSCLC, where managing the cancer might be as vital as reducing its size, due to the cancer's aggressive characteristics. The found statistical heterogeneity (I^2 = 61.0%) in DCR across trials necessitates an examination of individual variability and the intricate nature of disease response. This diversity may be ascribed to disparities in tumor biology, previous treatment history, disease stage at the commencement of Pembrolizumab therapy, or genetic variables affecting immunotherapy response. This indicates that although Pembrolizumab is generally successful, its efficacy varies, with specific patient subgroups potentially experiencing greater benefits than others. It underscores the significance of a tailored treatment approach, taking into account individual patient attributes, disease particulars, and potential genetic indicators that may forecast therapeutic response.

The 36% incidence of adverse events is a crucial factor in assessing the safety profile of Pembrolizumab. This suggests a significant percentage of patients encounter side effects; nonetheless, it is crucial to situate these results within the wider framework of oncology treatments, where balancing efficacy and adverse reactions remains a persistent challenge. The nature and intensity of these adverse events are essential for informing therapeutic decisions and patient guidance. Continuous oversight in observing and addressing these reactions, along with instructing patients on possible symptoms, is crucial for enhancing therapy results. Ongoing research into mitigation techniques and the identification of risk factors for serious adverse events will enhance the application of Pembrolizumab in clinical practice.

Numerous constraints must be recognized. The variability in study designs and patient demographics may affect the generalizability of the findings. Second, the incorporation of studies with differing follow-up periods may influence the evaluations of long-term efficacy and safety. Moreover, the majority of studies predominantly present short to medium-term results, with a deficiency in long-term survival data. The dependence on published data also introduces possible publication bias, although efforts to alleviate its effects. Finally, the inconsistency in PD-L1 expression and other biomarkers among trials was not uniformly addressed, with possible effects on therapy efficacy. These constraints underscore the necessity for more standardized, longitudinal, and extensive research to corroborate and enhance the conclusions reported.

Conclusions

Pembrolizumab exhibits notable efficacy and safety in treating advanced non-small cell lung cancer. The meta-analysis highlights its significant impact on diminishing tumor burden and managing disease progression, accompanied by an acceptable safety profile. Nevertheless, ongoing study and tailored treatment approaches are crucial to enhance its application and broaden its advantages for a wider patient demographic.

Disclosure of conflict of interest

None.

Address correspondence to: Zhouyi Lu, Department of Cardiothoracic Surgery, Huashan Hospital Affiliated to Fudan University, No. 12 Urumqi Middle Road, Jing'an District, Shanghai 200040, China. E-mail: zhouyi_lu@hotmail.com; Dr. Hong Pan, Department of Oncology, Chinese People's Liberation Army Western Theater General Hospital, No. 270, Rongdu Avenue, Jinniu District, Chengdu 610083, Sichuan, China. E-mail: hongpan88@163.com

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