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Comprehensive evaluation of treatment strategies for PD-L1 negative advanced non-small cell lung cancer: A network meta-analysis and survival comparison using reconstructed survival curves

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 September 2024 and was last updated on 18 September 2024.

INTRODUCTION

Review question / Objective To evaluate the efficacy of different first-line treatment strategies for programmed death-ligand 1 (PD-L1)-negative advanced non-small cell lung cancer (NSCLC) using network meta-analysis (NMA) and survival curve reconstruction (SCR) analysis.

Rationale Individual randomized controlled trials (RCTs) have provided insights into the relative benefits of these approaches, the optimal treatment strategy remains uncertain due to the lack of direct head-to-head comparisons between treatments for PD-L1 negative NSCLC patients. Several recent meta-analyses have addressed PD-L1-negative patients, but our network meta-analysis (NMA) incorporates a larger number of RCTs and a greater sample size of PD-L1-negative patients, ensuring robust statistical power. We plan to evaluate the efficacy of different first-line treatment strategies for PD-L1-negative advanced NSCLC using NMA and SCR analysis and conduct sub-group analyses based on different histological types. Through this comprehensive approach, we aim to provide a robust comparison of available treatments, thereby informing clinical practice and improving patient outcomes.

Condition being studied Patients with PD-L1-positive or high-expressing advanced NSCLC often experience improved OS and PFS when treated with ICIs . These patients typically show better responses to monotherapy with ICIs, reflecting the more favorable tumor microenvironment (TME) characterized by higher levels of PD-L1 expression, increased T-cell infiltration, and greater neoantigen burden. This underscores the importance of stratifying patients based on PD-L1 expression levels to optimize treatment outcomes. In contrast, patients whose tumors do not express PD-L1 (PD-L1-negative) represent a particularly challenging subgroup due to the limited efficacy of ICIs in this setting [19]. These patients often have poorer outcomes and face a higher risk of disease progression and mortality. However, recent trials have shown

promising results with the combination of chemotherapy (CT) and ICIs in advanced NSCLC, even in PD-L1-negative patients . The combined analysis of KEYNOTE-021 G, KEYNOTE-189, and KEYNOTE-407 showed that pembrolizumab plus chemotherapy significantly prolonged OS and PFS in patients with PD-L1-negative NSCLC compared to chemotherapy alone, across both global and Asian populations . Interestingly, dual immunotherapy combining anti-PD-1 and anti-CTLA-4 antibodies has also improved OS over chemotherapy, with a more pronounced benefit in the PD-L1-negative subgroup.

METHODS

Search strategy The search strategy combined terms related to "non-small cell lung cancer," "PD-L1 negative," and "first-line treatment" using appropriate Boolean operators.

Participant or population Previously untreated patients diagnosed with unresectable, locally advanced, recurrent, or metastatic NSCLC, either non-squamous or squamous, with PD-L1 negative expression.

Intervention Studies included at least one or more of the following treatment strategies: CT alone, PD-1/PD-L1 inhibitors + CT, BEV + CT, dual immunotherapy (PD-1/PD-L1 inhibitors + CTLA-4 inhibitors) with or without CT, and combination therapy of PD-1/PD-L1 inhibitor with BEV and CT.

Comparator Comparisons between different combination therapies for PD-L1 negative patients.

Study designs to be included Prospective RCTs.

Eligibility criteria Exclusion criteria were as follows: data on PD-L1-negative NSCLC patients in the study population could not be separated from the full cohort of patients; studies did not address the treatment strategies listed above or the treatment regimens were poorly described and could not be effectively compared with other studies; non-original research data such as reviews, commentaries, conference abstracts, case reports, animal studies, or in vitro studies; duplicate reports of published studies, unless the latter provided new or more detailed data; and serious flaws in the study design or inadequate and non-transparent data reporting to ensure the accuracy and reliability of the data.

Information sources The search covered databases including PubMed, EMBASE and the Cochrane Library.

Main outcome(s) Primary outcomes for the PD-L1 negative NSCLC patients were PFS, OS, ORR, DOR, and HR values.

Data management Two authors independently screened titles, abstracts, and full-text articles, and disagreements were resolved by a third researcher.

Quality assessment / Risk of bias analysis Study quality was assessed using the Cochrane Risk of Bias tool, focusing on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each criterion was categorized as high, low, or unclear risk. Investigators assessed each included study, recording the score or risk of bias level, to ensure the robustness and reliability of the analyses.

Strategy of data synthesis Direct comparisons were statistically analyzed using Stata 12.0 software (StataCorp LP, College Station, TX 77845, USA; 2011). Primary outcomes for the PD-L1 negative NSCLC patients (PFS, OS, ORR, DOR, and HR values) were summarized, with the I^2 statistic used to evaluate heterogeneity between studies.

Subgroup analysis For subgroup analyses, patients were categorized into three groups based on histologic types: all NSCLC patients excluding those from BEV-related RCTs ; non-Sq NSCLC patients; and Sq NSCLC patients.

Sensitivity analysis Sensitivity analyses were performed for the result of PFS/OS/ORR/DOR based ontheleave-one-out approach. The potential for publication bias in reported values were assessed using funnel plots, with the appropriate accuracy intervals.

Language restriction English.

Country(ies) involved China.

Keywords Non-small cell lung cancer, PD-L1-negative, network meta-analysis, progression-free survival, overall survival.

Contributions of each author

Author 1 - Jietao Ma - Author 1 drafted the manuscript.
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