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Neoadjuvant-Adjuvant versus Neoadjuvant-Only PD-1/PD-L1 Inhibitor in Completely Resected Non-Small-Cell Lung Cancer: A Systemic Review and Meta-analysisZhou, YX¹; Li, AL²; Yu, H³; Wang, YH⁴; Zhang, XY⁵; Qiu, HJ⁶; Du, W⁷; Luo, LF⁸; Fu, S⁹; Zhang, L¹⁰; Hongc¹¹.**ADMINISTRATIVE INFORMATION****Support** - This study was funded by grants 82272837, 81972898, 82172713 from the National Natural Science Funds of China; 2022A1515010386, 2023B1515020008 from Guangdong Basic and Applied Basic Research Foundation, 22ykqb15 from the Fundamental Research Funds for the Central Universities, Sun Yat-sen University, 2023A04J2130 from Guangzhou Basic and Applied Basic Research project.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2023120074**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2023 and was last updated on 18 December 2023.**INTRODUCTION**

Review question / Objective Neoadjuvant-adjuvant versus neoadjuvant-only anti-PD-(L)1 therapy in completely resected non-small cell lung cancer (NSCLC): Which is the preferred option?

Rationale This meta-analysis was designed to provide a comparison between the efficacy and safety profiles of neoadjuvant-adjuvant versus neoadjuvant-only anti-PD-(L)1 therapy in completely resected NSCLC.

Condition being studied The therapeutic landscape of resectable non-small cell lung cancer (NSCLC) has been reshaped by the emergence of immunotherapy. The CheckMate 816 trial

introduced PD-1 inhibitor solely in the neoadjuvant phase, while several recent trials explored neoadjuvant-adjuvant administration of PD-(L)1 inhibitor, leading to intense debates about the optimal perioperative immunotherapy strategies.

METHODS

Search strategy A comprehensive literature search was conducted across databases including PubMed, Embase, the Cochrane Library, supplemented by investigations from prominent oncology conferences, from database inception to July 31, 2023.

Participant or population Randomized controlled trials that investigated the neoadjuvant-adjuvant or

neoadjuvant-only application of PD-(L)1 inhibitor in resectable NSCLC.

Intervention Neoadjuvant-adjuvant anti-PD-(L)1 therapy in completely resected non-small cell lung cancer (NSCLC).

Comparator Neoadjuvant-only anti-PD-(L)1 therapy in completely resected non-small cell lung cancer (NSCLC).

Study designs to be included Randomized controlled trials that investigated the neoadjuvant-adjuvant or neoadjuvant-only application of PD-(L)1 inhibitor in resectable NSCLC.

Eligibility criteria Randomized controlled trials that investigated the neoadjuvant-adjuvant or neoadjuvant-only application of PD-(L)1 inhibitor in resectable NSCLC.

Information sources A comprehensive literature search was conducted across databases including PubMed, Embase, the Cochrane Library, supplemented by investigations from prominent oncology conferences, from database inception to July 31, 2023.

Main outcome(s) event-free survival (EFS), overall survival (OS) and treatment-related adverse events (TRAEs).

Additional outcome(s) Not applicable.

Quality assessment / Risk of bias analysis We gauged the methodological integrity of the incorporated trials utilizing the Cochrane Risk of Bias Tool.

Strategy of data synthesis The pooled hazard ratios (HRs) for both EFS and OS were determined through the generic inverse-variance methods model, while pooled relative risks (RRs) for TRAEs were derived via the Mantel-Haenszel method. Inter-trial heterogeneity was examined through Cochran's Q test, with P50% demarcating significant heterogeneity – in such instances, a random-effects model was enlisted; otherwise, a fixed-effects model was employed. Publication bias was assessed by scrutinizing the funnel plot of each trial's effect size against its reciprocal standard error, bolstered by the Egger test. Using Arm C as a fulcrum, indirect comparison between Arm A and Arm B was conducted using frequentist methodologies with the formula: $\log HR_{AB} = \log HR_{AC} - \log HR_{BC}$, and its standard error (SE) for the $\log HR$ was $SE = \sqrt{[SE(\log HR_{AC})]^2 + [SE(\log HR_{BC})]^2}$. Relative risk was analogously computed.

($\log HR_{BC}$)²). Relative risk was analogously computed.

Subgroup analysis The analysis method was the same as the strategy for data synthesis.

Sensitivity analysis Not applicable.

Language restriction English.

Country(ies) involved China.

Keywords Neoadjuvant-Adjuvant, Neoadjuvant-Only, PD-1/PD-L1 Inhibitor, Resected Non-Small-Cell Lung Cancer.

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