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Corresponding author:
YuanJia Hu

yuanjiahu@um.edu.mo

Author Affiliation:
State Key Laboratory of Mechanism and Quality of Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao SAR,China.

Comparative Efficacy of Domestic versus Imported PD-1/PD-L1 Inhibitor-Based Combinations as First-Line Therapy for Advanced NSCLC in China: A Systematic Review and Network Meta-Analysis

Yang, JT; Min, R; Hu, YJ.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

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 10 December 2025 and was last updated on 10 December 2025.

INTRODUCTION

Review question / Objective The rapid proliferation of studies on PD-1/PD-L1 inhibitor combinations has led to some trials design redundancy. Numerous combinations trials compare PD-1/PD-L1 inhibitors with chemotherapy, while direct comparison between immunotherapy combinations remain limited. Previous network meta-analyses covered only a portion of anti-PD-1/PD-L1 combination therapies, and some of the included study data no longer reflect contemporary clinical practice. To address these gaps, this study plan to conduct a comprehensive and updated systematic review of combination therapy trials encompassing all PD-1/PD-L1 inhibitors approved globally and in China for first-line treatment of advanced NSCLC, compared efficacy outcomes in a Bayesian framework, with subgroup analyses conducted by PD-L1 expression levels and histological types to refine treatment effects estimates across different patient populations. This objectives are to provide up-to-date, evidence-based recommendations for clinical practice to optimize treatment selection across diverse patient populations and affordability, and to offer insights to guide future clinical trials design of combinations therapies to improve the efficiency and precision of PD-1/PD-L1 inhibitor combinations development, furthermore to evaluate whether China domestic developed PD-1/PD-L1 inhibitors offer efficacy comparable to imported counterparts, to provide more accessible and affordable treatment options to NSCLC patients, ultimately to address unmet clinical needs and improve patients outcomes.

Rationale Advanced non-small cell lung cancer (NSCLC) imposes a heavy global burden, with unmet needs for optimal first-line PD-1/PD-L1

inhibitor combination therapies. This study aimed to comprehensively compare the efficacy of approved PD-1/PD-L1 inhibitor combinations, including China-developed agents, to provide evidence-based treatment recommendations.

Condition being studied Non-small cell lung cancer NSCLC; Immunotherapy; Combination Therapies.

METHODS

Search strategy A comprehensive search will be conducted across multiple databases and sources. Initial searches were performed on ClinicalTrials.gov using PD-1/PD-L1 inhibitors approved in China in "Intervention/treatment" and "NSCLC" in "Condition/disease". Supplementary searches include PubMed, Google Scholar, and abstracts from American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), and European Society of Medical Oncology (ESMO) using NCT codes of preliminarily screened trials.

Participant or population To include patients with histologically or cytologically confirmed advanced NSCLC (stage III-IV) in Interventional clinical trials, with any level of PD-L1 expression, that used PD-1 or PD-L1 inhibitor combinations as first-line treatment settings, comparing with other treatment modalities, reporting at least one of the following clinical outcomes:
Overall survival (OS), defined as the time from randomization until death from any cause; or Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death, whichever occurs first.

Intervention The group of interventions are the approved PD-1 or PD-L1 inhibitor-based combination therapies regimens, including atezolizumab plus chemotherapy (atezo_chemo), atezolizumab plus bevacizumab plus chemotherapy (atezo_beva_chemo), camrelizumab plus chemotherapy (camre_chemo), cemiplimab plus chemotherapy (cemip_chemo), durvalumab plus tremelimumab (durva_treme), durvalumab plus chemotherapy (durva_chemo), durvalumab plus tremelimumab plus chemotherapy (durva_treme_chemo), durvalumab (durva), nivolumab plus ipilimumab (nivo_ipi), nivolumab plus ipilimumab plus chemotherapy (nivo_ipi_chemo), nivolumab plus bevacizumab plus chemotherapy (nivo_beva_chemo), pembrolizumab plus chemotherapy (pem_chemo), penpulimab plus chemotherapy (penpu_chemo), serplulimab plus chemotherapy (serpl_chemo), sintilimab plus chemotherapy (sint_chemo), sugemalimab plus chemotherapy (sugem_chemo), toripalimab plus chemotherapy (torip_chemo), tislelizumab plus paclitaxel (tisle_chemo), tislelizumab plus nab-paclitaxel (tisle_nab).

Comparator The comparative intervention are including chemotherapy (chemo), bevacizumab plus chemotherapy (beva_chemo), and durvalumab (durva) mono-therapy.

Study designs to be included Included studies are interventional randomized controlled trials (RCTs) of first-line PD-1/PD-L1 inhibitor combinations for histologically or cytologically confirmed Stage III–IV NSCLC that compared combinations with other treatments (any PD-L1 expression) and reported overall survival (OS) or Progression-free survival (PFS)PFS.

Eligibility criteria Published and unpublished trials that met the following criteria are included:
(1)Interventional clinical trials that included patients with histologically or cytologically confirmed advanced NSCLC (stage III-IV);
(2)RCTs that used PD-1 or PD-L1 inhibitor combinations as first-line treatment settings;
(3)Trials comparing PD-1 or PD-L1 combinations with other treatment modalities for patients with any level of PD-L1 expression;
(4)Trials reporting at least one of the following clinical outcomes:
a.Overall survival (OS), defined as the time from randomization until death from any cause;
b.Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death, whichever occurs first.
The following types of trials are excluded:
(1) Non-interventional trials;
(2) Terminated or withdrawn trials;
(3) Trials not yet recruiting patients;
(4) Trials with less than 10 subjects Test;
(5) Crossover test;
(6) RCTs with ambiguous clinical outcomes (e.g., unreported hazard ratio [HR]).

Information sources ClinicalTrials.gov database, PubMed, Google Scholar, and abstracts from American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), and European Society of Medical Oncology (ESMO).

Main outcome(s) 1. Overall survival (OS), defined as the time from randomization until death from any cause;

2. Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death, whichever occurs first.
3. Objective Response Rate (ORR), defined as the proportion of patients in a clinical trial whose tumor shrinks (partial response) or disappears completely (complete response) after treatment.
The primary outcomes are OS and PFS, and the secondary outcome is ORR. HRs (95% CIs) will be used as the effect sizes for OS and PFS, and ORs (95% CIs) for ORR.

Quality assessment / Risk of bias analysis Two investigators will independently extract data per PRISMA: hazard ratios (HRs) with corresponding 95% confidence intervals (95% CI) for OS and PFS; odds ratios (ORs) with 95% CIs for ORR; and trial details, including trial name, National Clinical Trial (NCT) number, first author, year of publication, phase, sample size, patient demographics, smoking status, histologic type, PD-L1 expression, Eastern Oncology Group (ECOG) performance status score, and data sources. The Cochrane Risk of Bias Tool (2.0) for RCTs will be used to assess potential bias, including the randomization process, intervention deviations, missing data, outcome measurement, and selection of the reported results, classifying each study as having low, high, or unclear risk. Discrepancies will be resolved through authors discussion.

Strategy of data synthesis A Bayesian Network Meta-Analysis (NMA) will be conducted using the gemtc package in R software (version 4.2.3) and JAGS, applying Markov chain Monte Carlo simulation methods to integrate direct and indirect evidence. A fixed-effects consistency model will be adopted with four Markov chains (20,000 burn-in iterations, 50,000 sample iterations). Convergence is assessed using trace plots and the Brooks–Gelman—Rubin diagnostic. Ranking probabilities for all treatment strategies are calculated using surface under the cumulative ranking (SUCRA) values (0 = least effective, 1 = most effective).

Subgroup analysis To enable a more precise assessment of the clinical effects of immune-oncology (IO) combination therapies, we will perform a stratified analysis based on patients' PD-L1 expression levels and histological type. This approach is intended to reduce heterogeneity within the study and enhance the reliability of the findings. Subgroup analyses will focus solely on two efficacy endpoints: overall survival (OS) and progression-free survival (PFS).
Stratification will be conducted as follows:

1. By PD-L1 expression level: patients will be divided into four subgroups: <1%, ≥1%, 1%–49%, and ≥50%.
2. By histological type: patients will be classified into two subgroups: non-squamous and squamous lung cancer.

Sensitivity analysis We will assess similarity, transitivity, and consistency via Bayesian meta-regression analyses (baseline characteristics: sample size, gender, age, ECOG score, smoking status, and metastases). Global inconsistency is evaluated by comparing consistency and inconsistency models, and local inconsistency is assessed using node-splitting. Heterogeneity between studies is estimated using the statistical inconsistency index (I^2) (50% = high; sensitivity analyses if high).

Language restriction No.

Country(ies) involved China.

Keywords PD-1/PD-L1 inhibitors; Non-small cell lung cancer NSCLC; Combination therapies; Network Meta-Analysis NMA.

Contributions of each author

Author 1 - Rui Min.
Email: minrui1122@sina.com
Author 2 - Jingting Yang.
Email: m13270710578@163.com
Author 3 - Yuanjia Hu.
Email: yuanjiahu@um.edu.mo