INPLASY PROTOCOL

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Corresponding author:
Shun Xu

shunxucmu@126.com

Author Affiliation:
Department of Thoracic Surgery, the First Affiliated Hospital of China Medical University

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None.

Association of Patient Sex with Efficacy of Programmed Death-1/ Ligand-1 Inhibitors in Advanced Non–small-cell Lung Cancer: A Systematic Review and Meta-analysis

Liu, S[1]; Zhang, X[2]; Yang, W[3]; Xu, S[4].

Review question / Objective: **Do women derive more advantage from programmed death-1/ligand-1 inhibitors, compared with standard systemic therapy, in the treatment of advanced non-small-cell lung cancer?**
Condition being studied: **Lung cancer remains the leading cause of cancer-related deaths around the world, accounting for nearly one fifth of such deaths (1). Non–small-cell lung cancer (NSCLC) is the most common type of lung cancer; 80% of lung cancers are NSCLC (2). Programmed death-1/ ligand-1 (PD-1/PD-L1) inhibitors, which overcome tumor-induced immunosuppression by blocking native immune regulators, show anti-tumor activity in the treatment of multiple cancers. With the application of PD-1/L1 inhibitors, remarkable progress has been made in the treatment of advanced NSCLC. There are many differences between women and men in immune response. Generally, women have stronger adaptive and innate immune responses than men do, which not only allow women to recover more quickly from infectious disease but also give them a higher response rate to vaccination than men. At the same time, however, three quarters of patients with systemic autoimmune diseases are women. It has been hypothesized that the differences in immune response between men and women could contribute to sex differences in cancer prevalence and mortality. In epidemiology, men have a significantly higher risk of cancer mortality than women, particularly in melanoma and lung cancers.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 January 2021 and was last updated on 2 January 2021 (registration number INPLASY202110005).

INTRODUCTION

Review question / Objective: **Do women derive more advantage from programmed death-1/ligand-1 inhibitors, compared with standard systemic therapy, in the treatment of advanced non-small-cell lung cancer?**

Rationale: **Whether sex-based differences in the survival benefits of PD-1/L1**

inhibitors exist remains controversial. In a systematic review and meta-analysis of randomized clinical trials (RCTs), Conforti et al. reported that male patients treated with PD-1/L1 inhibitors have a greater survival benefit than women. However, a systematic review conducted by Wallis et al. reported that the survival benefits are not sex-dependent. These systematic reviews included subgroup analyses of NSCLC but did not include further stratified analyses. Moreover, several RCTs investigating the efficacy of PD-1/L1 inhibitors in patients with advanced NSCLC were recently published. Therefore, we need a systematic review and meta-analysis to explore the association of patient sex with survival benefits derived from PD-1/L1 inhibitors in patients with advanced NSCLC.

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METHODS

Search strategy: We will search PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov for original articles from inception to June 30, 2020.

Participant or population: Patients with non-small-cell lung cancer.

Intervention: PD-1/L1 inhibitor monotherapy or immunotherapy-based combination therapy.

Comparator: Standard systemic therapy.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: In accordance with the Population, Intervention, Comparison, Outcomes and Study (PICOS) approach, RCTs meeting the following criteria will be included: population, patients with advanced NSLCLC; intervention, PD-1/L1 inhibitor monotherapy or immunotherapy-based combination therapy; comparison, standard of care for advanced NSCLC (platinum-based chemotherapy or docetaxel chemotherapy); and outcomes, overall survival (OS) stratified by patient sex.

Information sources: Electronic databases and abstract from conferences.

Main outcome(s): Overall survival (OS) stratified by patient sex.

Data management: Two investigators will independently perform data extraction, and discrepancies among reviewers will be resolved by consensus. From each study we will extract the title, year of publication, study phase, lines of therapy, intervention, number of patients, median age, sex distribution, follow-up time, National Clinical Trial (NCT) number, and hazard ratio (HR) and 95% confidence interval (CI) for death stratified by patient sex. When two or more studies reported a duplicate population, we will extract the most complete and up-to-date data.

Quality assessment / Risk of bias analysis: We will assess potential risks of bias of the included trials using the Cochrane risk-of-bias tool. Quality assessment consisted of random-sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective report (reporting bias), and other biases. Included studies will be categorized into three grades: low risk of bias (+), high risk of bias (–), and unclear (?). The quality assessment will be conducted by two independent investigators, and any discrepancy among investigators will be resolved by consensus.

Strategy of data synthesis: The primary endpoint of this systematic review is the difference in effectiveness of PD-1/L1 inhibitors between male and female patients, as evaluated by HR for OS. For the time-to-event variables (HR), we will apply the inverse variance-weighted method to calculate pooled P-values and 95% CIs. We used the DerSimonian–Laird method to test heterogeneity between the two estimates and I2 values to quantify heterogeneity. In addition, between-study heterogeneity will be estimated using Dixon's Q test and the I2 statistic. The fixed-effect model will be considered if significant heterogeneity was observed (I2 ≤50%); otherwise, the random-effect model was applied. P = 0.05 will be considered to indicate statistical significance. We will perform all statistical analysis using STATA software version 15.0 (StataCorp., College Station, TX, USA).

Subgroup analysis: We will conduct prespecified subgroup analysis to evaluate the potential effects of methodological factors on the effectiveness of PD-1/L1 inhibitors. Subgroups based on the following factors will be considered: line of treatment, types of immunotherapeutic drugs (PD-1 inhibitor and PD-L1 inhibitor), study methodology (PD-1/L1 inhibitor, PD-1/L1 inhibitor plus chemotherapy), and proportion of women in each study (40%).

Sensibility analysis: Not available.

Language: English.

Country(ies) involved: China.

Keywords: programmed death-1/ligand-1 inhibitors; non–small-cell lung cancer; immunotherapy; systematic review; meta-analysis.

Contributions of each author:

Author 1 - Shu Liu contributed to study selection, data extraction, quality assessment, statistical analysis and drafting of the manuscript.
Email: shuliulll@sina.com
Author 2 - Xin Zhang contributed to study selection, data extraction, quality assessment, statistical analysis and drafting of the manuscript.
Email: zhangxin7@cmu1h.com
Author 3 - Wenhan Yang contributed to data acquisition, data interpretation.
Email: 13677074595@163.com
Author 4 - Shun Xu contributed to the study design and revision of the manuscript.
Email: shunxucmu@126.com