INPLASY PROTOCOL

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None declared.

Concomitant statins and the survival of patients with non-small cell lung cancer treated with immune checkpoint inhibitors: a meta-analysis

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Review question / Objective: **To systematically evaluate the effect of concomitant statins in patients with non-small cell lung cancer patients receiving immune checkpoint inhibitors.**
Condition being studied: **Statins are suggested to improve cancer survival by possible anti-inflammatory effect. However, it remains unclear if concomitant use of statins could improve the efficacy of immune checkpoint inhibitors (ICIs) in patients with non-small cell lung cancer (NSCLC). Accordingly, a meta-analysis was performed to systematically evaluate the effect of concomitant statins in NSCLC patients receiving ICIs.Patients with confirmed diagnosis of NSCLC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 May 2022 and was last updated on 17 May 2022 (registration number INPLASY202250110).

INTRODUCTION

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Rationale: **Immune checkpoint inhibitors (ICIs) are a group of novel anticancer agents which showed substantial therapeutic efficacy in patients with various solid cancers, including patients with non-small cell lung cancer (NSCLC). However, previous studies also showed that therapeutic responses to ICIs varied among patients with cancer. Accordingly, previous meta-analyses of observational studies have shown that statin use may favorably affect the survival of patients with lung cancer. However, none of the included**

studies in these meta-analyses including NSCLC patients treated with ICIs. Therefore, this meta-analysis was conducted aiming to systematically evaluate the effect of concomitant statins on the therapeutic efficacy of ICIs in patients with NSCLC.

Condition being studied: Statins are suggested to improve cancer survival by possible anti-inflammatory effect. However, it remains unclear if concomitant use of statins could improve the efficacy of immune checkpoint inhibitors (ICIs) in patients with non-small cell lung cancer (NSCLC). Accordingly, a meta-analysis was performed to systematically evaluate the effect of concomitant statins in NSCLC patients receiving ICIs.Patients with confirmed diagnosis of NSCLC

METHODS

Search strategy: ("statin" OR "3-hydroxy-3-methyl-glutarylCoA reductase inhibitor" OR "CS-514" OR "statin" OR "simvastatin" OR "atorvastatin" OR "fluvastatin" OR "lovastatin" OR "rosuvastatin" OR "pravastatin" OR "pitavastatin") AND "lung cancer" AND ("survival" OR "mortality" OR "prognosis" OR "death" OR "recurrence" OR "collapse").

Participant or population: Adult patient with NSCLC receiving ICIs, including PD-1/PD-L1 inhibitors, CTLA4 inhibitors, or their combination.

Intervention: Patients with concomitant use of statins.

Comparator: Patients without concomitant use of statins.

Study designs to be included: Cohort studies.

Eligibility criteria: P (patients): Adult patient with NSCLC receiving ICIs, including PD-1/PD-L1 inhibitors, CTLA4 inhibitors, or their combination;I (exposure): patients with concomitant use of statinsC (control): patients without concomitant use of statinsO (outcomes): progression-free survival (PFS) and/or overall survival (OS) between users and nonusers of statins; reported as relative risk;S (study design): cohort studies.

Information sources: PubMed, Embase, and Web of Science.

Main outcome(s): progression-free survival (PFS) and/or overall survival (OS) between users and nonusers of statins; reported as relative risk.

Data management: Two independent authors conducted literature search and analysis, data collection, and study quality assessing separately. If discrepancies were encountered, the corresponding author joined the discussion for final judgement. Data of study information, patient demographic factors, types of ICIs, definition of concurrent statin application, outcomes reported, and analytic methods were collected.

Quality assessment / Risk of bias analysis: Study quality assessment was achieved via the Newcastle–Ottawa Scale with scoring regarding the criteria for participant selection, comparability of the groups, and the validity of the outcomes. The scale ranged between 1-9 stars, with larger number of stars presenting higher study quality.

Strategy of data synthesis: The main objective was to determine the influence of concomitant statin on survival of patients with NSCLC on treatment of ICIs, which was presented with hazard ratios (HRs) as well as their confidence intervals (CIs). Using the 95% CIs or P values, Data of RRs and the standard errors (SEs) could be calculated, and a subsequent logarithmical transformation was conducted to keep stabilized variance and normalized distribution (26). Between study heterogeneity was estimated with the Cochrane's Q test and the I2 statistic(28), with I2 > 50% reflecting the significant heterogeneity. A random-effect model was applied to combine the results by incorporating the influence of heterogeneity (26). We observed the

influence of each study on the overall results by performing sensitivity analyses which omitted one study at a time (29). Subgroup analyses were also performed to explore the different analytic model of the study on the outcome. By construction of the funnel plots, the publication bias was estimated based on the visual judgement of the symmetry of the plots, supplemented with the Egger's regression asymmetry test (30). The RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) software package was applied for these analyses.

Subgroup analysis: Subgroup analyses were also performed to explore the different analytic model of the study on the outcome.

Sensitivity analysis: We observed the influence of each study on the overall results by performing sensitivity analyses which omitted one study at a time.

Language: No restriction.

Country(ies) involved: China.

Keywords: Statins; Immune checkpoint inhibitors; Non-small cell lung cancer; Survival; Meta-analysis.

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