INPLASY PROTOCOL

To cite: Lai et al. Sex and the efficacy of immunotherapy in malignancy. Inplasy protocol 202120071. doi: 10.37766/inplasy2021.2.0071

Received: 21 February 2021

Published: 21 February 2021

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Support: **No. 20203122.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Sex and the efficacy of immunotherapy in malignancy

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Review question / Objective: **To assesse the efficacy of immunotherapy in advanced melanoma according to patient sex.To examine the association of patient sex with the advantages of immunotherapy in patients with advanced cancer.**
Condition being studied: **A series of costimulatory, coinhibitory receptors and their ligands, known as immune checkpoints, control these processes. Among them, the cytotoxic T-lymphocyte protein 4 (CTLA-4) and programmed cell death 1 (PD-1) pathways are significant therapeutic targets. Not only do they play a key role in immune homeostasis under physiological conditions, but they can also be a mechanism for carcinoma cells to escape immune surveillance.However, the sex difference in the efficacy of immune checkpoint inhibitors for malignancy is unknown.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 February 2021 and was last updated on 21 February 2021 (registration number INPLASY202120071).

INTRODUCTION

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physiological conditions, but they can also be a mechanism for carcinoma cells to escape immune surveillance.However, the sex difference in the efficacy of immune checkpoint inhibitors for malignancy is unknown.

METHODS

Search strategy: We will search articles in three electronic database including PubMed, EMBASE and Cochrane Library. All the English publications until 10 March 2021 will be searched without any restriction of countries or article type. Reference list of all selected articles will independently screened to identify additional studies left out in the initial search.

Participant or population: 1.Randomised trials which assess inhibitors of PD-1, CTLA-4, or their combination, in patients with cancer; 2.Randomised trials had to have data available for the hazard ratio(HR) for death according to patients' sex. Exclusion criteria: 1.Single-arm phase 1 and 2 trials; 2.Retrospective or prospective observational cohort studies or reported subgroup analysis for one sex only.

Intervention: The main intervention: inhibitors of PD-1, PD-L1, CTLA-4, or their combination.

Comparator: Non-exposed control group: Other systemic treatment regimens including chemotherapy, placebo or non-immunological drugs.

Study designs to be included: Randomized controlled trials (RCTs) will be included.

Eligibility criteria: Inclusion criteria: 1.Randomised trials which assess inhibitors of PD-1, CTLA-4, or their combination, in patients with cancer; 2.Randomised trials had to have data available for the hazard ratio(HR) for death according to patients' sex. Exclusion criteria: 1.Single-arm phase 1 and 2 trials; 2.Retrospective or prospective observational cohort studies or reported subgroup analysis for one sex only.

Information sources: We will search articles in three electronic database including PubMed, EMBASE and Cochrane Library.

Main outcome(s): Overall survival (OS). Effect measure: hazard ratio(HR).

Additional outcome(s): Progression-free survival (PFS).

Data management: Two authors will independently extract data. Any disagreement will be resolved by discussion until consensus is reached or by consulting a third author.The following data will be extracted: author, year of publication, study period, original inclusion criteria, total number of people included in the study, doses of immune checkpoint inhibitors.

Quality assessment / Risk of bias analysis: The risk of bias will be assessed using the Cochrane Collaboration's tool. The evaluation criteria of Cochrane Handbook have seven aspects.The evaluation criteria are 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 outcome reporting (reporting bias), and other sources of bias.

Strategy of data synthesis: The heterogeneity was identified using Cochrane's Q and I^2 statistic. For the Q test, P-value less than 0.10 implied significant heterogeneity; for the I2 statistic, I2 value more than 50% indicated significant heterogeneity. Random effects model will be used, and analysis will be performed with Stata version 14.0.

Subgroup analysis: The subgroup analysis include cancer histologic type and target of intervention agents.The subgroup analysis will be tested with a χ^2 test.

Sensitivity analysis: **In order to detect heterogeneity, we will conduct sensitivity analysis.**

Language: **English.**

Country(ies) involved: **China.**

Keywords: **Immunotherapy, cancer, meta-analysis.**

Contributions of each author:
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