INPLASY PROTOCOL

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Conflicts of interest:
None.

A meta-analysis of immune-related adverse events via anti- Programmed Death 1 treatment in malignant tumors

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Review question / Objective: **The aim of this meta-analysis is to investigate the immune-related adverse events via anti-Programmed Death 1 treatment in malignant tumors.**
Condition being studied: **Due to the significant impact of anti-PD-1 treatment on improving the survival of several advanced cancers, the use of it will be inevitably increased in the future. It is imperative to identify the incidence and characteristics of irAEs in malignant tumors after anti-PD-1 treatment. Here, we plan to conduct a meta-analysis to investigate the incidence of irAEs via anti-PD-1 treatment in malignant tumors.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 January 2021 and was last updated on 23 January 2021 (registration number INPLASY202110091).

INTRODUCTION

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METHODS

Participant or population: Patients diagnosed with malignant tumors, including melanoma, Hodgkin lymphoma, urothelial carcinoma, breast cancer, squamous cell carcinoma of head and neck (SCCHN), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, etc will be included.

Intervention: Patients receiving anti-PD-1 treatment.

Comparator: Patients receiving docetaxel or methotrexate treatment.

Study designs to be included: Prospective cohort studies or randomized controlled trials will be included.

Eligibility criteria: (1) animal experiments; (2) receiving anti-PD-1 drugs in combination with other drugs; (3) researches not related to our topic; (4) articles incapable to extract data; (4) case reports, letters, abstracts, meta-analyses or reviews.

Information sources: The PubMed, Embase, Cochrane Library and Web of Science databases will be searched for identifying relevant trails. The terms included are shown as follows: "anti-PD-1" OR "anti-programmed death-1" OR "Nivolumab" OR "Opdivo" OR "ONO-4538" OR "ONO 4538" OR "ONO4538" OR "MDX-1106" OR "MDX 1106" OR "MDX1106" OR "BMS-936558" OR "BMS 936558" OR "BMS936558" OR "Pembrolizumab" OR "SCH-900475" OR "Keytruda" OR "MK-3475" OR "lambrolizumab" OR "Tislelizumab" AND "safety" OR "security" OR "side effects" OR "adverse effects" OR "adverse events".

Main outcome(s): Total global incidence of irAEs A total of 38 articles will include the data about the global incidence of irAEs. Substantial heterogeneity will be observed in these studies (I2=93.6%), so the random-effect model will be used for pooled analysis. The overall global incidence of irAEs was 27% (95%CI: 22.4%-31.6%). The global incidence of irAEs was 42.0% (95%CI: 30.5%-53.4%) with nivolumab and 18.0% (95%CI: 15.6%-20.5%) with pembrolizumab. Global incidence of irAEs of severe grade There were 32 studies presenting the data about global incidence of irAEs of severe grade. No statistically significant difference was shown according to the results from the heterogeneity test (I2=47.5%), so fixed-effect model was used for pooled analysis. The results delineated that the overall global incidence of irAEs of severe grade was 4.7% (95%CI: 4.0%-5.3%). The global incidence of irAEs of severe grade was 5.4% (95%CI: 4.5%-6.3%) with nivolumab and 4.0% (95%CI: 3.1%-4.9%) with pembrolizumab.

Quality assessment / Risk of bias analysis: For cohort studies, the modified Newcastle-Ottawa Scale (NOS) system (total score: 10 points) will be used for assessing the quality of the articles. According to this scale, the higher the score, the higher the quality. Studies with a score <5 are in low quality and ≥5 in high quality. The modified Jadad scale will be used to evaluate the quality of RCTs (total score: 7) with 1-3 as low quality and 4-7 as high quality.

Strategy of data synthesis: Statistical analysis will be performed using Stata15.1 software (Stata Corporation, College Station, TX, USA). Incidence with 95% confidence intervals (CIs) will be used as the effect index. Heterogeneity test will be carried out for all indicators. Heterogeneity I2≥50% will be subjected to random-effect model analysis while I2<50% will be analyzed via fixed-effect model. When the heterogeneity was substantial (I2≥50%), subgroup analysis will be conducted in terms of drug, tumor type and study type. Sensitivity analysis will be performed on all outcomes and publication bias will be detected via Begg's test. When there are publication bias, Trim and Fill method will be adopted to correct publication bias and

adjust the effect size. P<0.05 will be considered statistically significant.

Subgroup analysis: In this meta-analysis, the incidence of patients with malignant tumors treated with anti-PD-1 will be analyzed with regards to different organs, cancers, drugs and doses of drugs. Skin, endocrine system and gastrointestinal tract related irAEs may have a higher incidence during the treatment of anti-PD-1. The incidence of irAEs may be the highest in melanoma patients.

Sensitivity analysis: Sensitivity analysis will be performed on severe grade and any grade.

Country(ies) involved: China.

Keywords: anti-PD-1; immune-related adverse events; malignant tumors.

Contributions of each author:

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