INPLASY PROTOCOL

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Support: **Not applicable.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
Not applicable.

Differences of dermatological adverse events associated with anti-PD-1, anti-PD-L1, anti-CTLA-4: a systematic review and meta-analysis

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Review question / Objective: **What are the differences of dermatological immune-related adverse events among anti-PD-1, anti-PD-L1, anti-CTLA-4? We aim to generate a clinically useful summary of the characteristics, frequency and spectrum.**
Condition being studied: **The emergence of immune checkpoint inhibitors (ICIs) has revolutionized cancer therapy, which profoundly improves the prognosis of pan-cancer patients. Meanwhile, ICIs could trigger immune-related adverse events (irAEs), of which dermatological toxicities are the most common irAEs. The better understanding of dermatological irAEs of ICIs enables us to recognize, handle, and prevent at an earlier stage.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 April 2020 and was last updated on 29 April 2020 (registration number INPLASY202040205).

INTRODUCTION

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METHODS

Search strategy: We will search ClinicalTrials.gov, PubMed, Embase, Cochrane Library for randomized controlled trials (RCTs) of immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and anti-CTLA-4, which were published between January 2010 and March 2020.

Participant or population: Inclusion criteria: patients who were treated with ICIs in randomized controlled trials. Exclusion criteria: patients who were high-risk for irAEs, for instance, patients with underlying autoimmune disease, chronic viral infection, and organ or hematopoietic stem-cell transplants.

Intervention: The immune checkpoint inhibitors are the main interventions, which include anti-PD-1, anti-PD-L1, anti-CTLA-4 monotherapy, or in combination with chemotherapy, targeted therapy, radiotherapy.

Comparator: The comparators mainly comprise chemotherapy, targeted therapy, radiotherapy, and placebo. The combination of ICIs or other types of immunotherapy will be excluded.

Study designs to be included: Randomized controlled trials will be included.

Eligibility criteria: (1) the dermatological adverse events of ICIs monotherapy were specifically declared; (2) clearly listed the cases or incidence of safety profiles with specific grade.

Information sources: ClinicalTrials.gov PubMed, Embase, Cochrane Library and the abstrct from conference proceedings.

Main outcome(s): The incidence of dermatological adverse events of anti-PD-1, anti-PD-L1, and anti-CTLA-4, which include monotherapy or in combination with other treatments, such as chemotherapy, targeted therapy.

Data management: Clinical trial names, first author, recruitment year, published year, ClinicalTrials.gov identifier, study phase, trial design, type of cancer, dosage, and administration of ICIs, number of participants, lines of previous therapy, PD-L1 status, interventional and controlled management, follow-up time, the number of responders and incidence of irAEs, hazard ratio (HR) and 95% confident interval (CI) of both PFS and OS will be extracted.

Quality assessment / Risk of bias analysis: Using the Cochrane Collaboration Handbook (version 5.1.0), selection bias, performance bias, attribution bias, and detection bias will be consecutively evaluated. The statistical heterogeneity will be assessed using the I^2 statistic, in which an I^2 value < 50% was regarded as acceptable.

Strategy of data synthesis: A network meta-analysis, with the design of mixed treatment comparisons (MTC), will be conducted for comparative incidences of dermatological irAEs among three groups of ICIs. A Bayes random-effect framework will be utilized to validate models with Markov Chain Monte Carlo (MCMC) methods, by the motivation of JAGS software version 4.3.0. The relative rates of dermatological irAEs, as the dichotomous variables, will be indicated by the pooled risk ratio (RR) and 95% credible interval (CrI).

Subgroup analysis: Subgroup analysis will be performed stratified by treatment, including monotherapy, chemotherapy, targeted therapy. The inclusion of studies and participants will depend on the interventions.

Sensibility analysis: Sensibility analysis will be conducted by metafor package of R software.

Language: English.

Country(ies) involved: China.

Keywords: immune checkpoint inhibitors; dermatological toxicities; adverse events; network meta-analysis.

Contributions of each author:

Author 1 - Yiqun Han - Yiqun Han will draft the manuscript and conduct the meta-analysis.

Author 2 - Binghe Xu - Binghe Xu will conduct the meta-analysis and develop the methodology.

Author 3 - Jiayu Wang - Jiayu Wang will extract data and check the inconsistency.