

INPLASY PROTOCOL

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**Review Stage at time of this
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Conflicts of interest:
None.

Geographic heterogeneity in the outcomes of patients receiving immune checkpoint inhibitors for advanced solid tumors: a systematic review and meta-analysis

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Review question / Objective: Is region associated with clinical efficacy in patients with solid tumors treated with immune checkpoint inhibitors (ICIs)?

Condition being studied: Immune checkpoint inhibitors (ICIs) have radically changed the treatment modalities for a wide range of tumor types. Little is known about the effect of geographic location on efficacy of ICIs. We aim to investigate whether there is a region-dependent influence on patients with solid tumors treated with ICIs.

Information sources: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to October 2019. We also expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles could be screened. Finally, references to the studies included in the final selection were also checked.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 May 2020 and was last updated on 15 May 2020 (registration number INPLASY202050062).

INTRODUCTION

Review question / Objective: Is region associated with clinical efficacy in patients with solid tumors treated with immune checkpoint inhibitors (ICIs)?

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influence on patients with solid tumors treated with ICIs.

METHODS

Search strategy: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to October 2019. The following keywords were used: “neoplasm”, “malignant neoplasm”, “carcinoma”, “nivolumab”, “pembrolizumab”, “cemiplimab”, “pidilizumab”, “cetrelimab”, “camrelizumab”, “toripalimab”, “sintilimab”, “tislelizumab”, “durvalumab”, “atezolizumab”, “avelumab”, “bintrafusp alfa”, “envafolimab”, “ipilimumab”, “randomized controlled trial.” Finally, references to the studies included in the final selection were also checked. There is no language limitation in the literature search.

Participant or population: We included patients with advanced or metastatic solid tumors who have been enrolled in phase III randomized controlled trials of ICIs. We explored the efficacy of ICIs based on three designated regions which are North America, Europe, and Asia, respectively. Studies that were not provided with specific data would be excluded.

Intervention: The immune checkpoint inhibitors are the main interventions, including anti-PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab, pidilizumab, cetrelimab, camrelizumab, toripalimab, sintilimab, tislelizumab), anti-PD-L1 inhibitors (durvalumab, atezolizumab, avelumab, bintrafusp alfa, envafolimab), anti-CTLA-4 inhibitors (ipilimumab, tremelimumab). ICIs could be applied as monotherapy or in combination with other drugs.

Comparator: The efficacy of ICIs could be compared with placebo, chemotherapy, targeted therapy, and immunotherapy. The control regimen cannot include ICI unless it is a standard therapy.

Study designs to be included: Only phase III randomized controlled trials were included.

Eligibility criteria: (1) phase III randomized controlled trial (RCT) (2) In the experimental arm, ICIs (anti-PD-1 inhibitors or anti-PD-L1 inhibitors or anti-CTLA-4 inhibitors) were applied alone or in combination with other drugs, either immunological drug or chemotherapy. (3) The control regimen cannot include ICI unless it is a standard therapy. (4) Studies provided efficacy data of patients from North America, Europe, and Asia, respectively, and the data was required to include hazard ratio (HR) and 95% confidence interval (CI) of overall survival (OS) or progression-free survival (PFS).

Information sources: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to October 2019. We also expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles could be screened. Finally, references to the studies included in the final selection were also checked.

Main outcome(s): The main outcome was to assess the difference in efficacy of ICIs based on region. The main outcome of this review was the overall survival (OS) of the patients from three designated geographic regions.

Additional outcome(s): The additional outcome of this review was the progression-free survival (PFS) of the patients from three designated geographic regions.

Data management: The following information was acquired from the selected studies: (1) Study characteristics: publication year, first author, study design, setting line of treatment, type of cancer, and treatment regimens of each study arm. (2) Study population: median age, age

range, and number of patients treated in each study arm. (3) Study outcomes: HR and 95% CI for OS and/or PFS in the overall population, HR and 95% CI for OS and/or PFS in patients from North America, Europe, and Asia. Two investigators (Manyu Li, Jiannan Yao) independently extracted data from the studies, and all disagreements were resolved via discussion or consultation with the third investigator (Guangyu An).

Quality assessment / Risk of bias analysis:

The study quality was evaluated using the Cochrane Collaboration's "Risk of bias" tool. The criteria included randomized sequence generation, allocation concealment, blinding of patients, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. We designated the risk of each item as low, high, or unclear. Two authors independently assessed the risk of bias, and all discrepancies were resolved by discussion with the third author until achieving consensus among the three authors.

Strategy of data synthesis: The pooled HR and 95% CI of OS and PFS for patients from Asia, Europe, and North America were calculated, with HR<1.0 manifesting a better outcome in the experimental arm. We used the Q test and I² statistics to assess the heterogeneity among the RCTs. When the two primary indicators are in specific ranges (P>0.1 and I²<50%), it was considered to show that no significant heterogeneity could be found between studies, and the fixed-effect model should be applied. If there was significant heterogeneity between the studies (P>50%), we analyzed them through the random-effects model. To explore the source of heterogeneity, subgroup analysis was carried out according to the class of ICIs, the type of ICIs, cancer type, and the setting line of treatment where possible. Publication bias was assessed by funnel plots. Furthermore, Begg's and Egger's tests were utilized to examine the publication bias across studies. Sensitivity analysis was utilized to examine whether

the results could have been influenced by a single study by removing one study at a time. Our meta-analysis was performed using Review Manager 5.3 and STATA 14 software. For combined analysis, a P < 0.05 was treated as statistically significant.

Subgroup analysis: To explore the source of heterogeneity, subgroup analysis was carried out according to the class of ICIs, the type of ICIs, cancer type, and the setting line of treatment where possible.

Sensibility analysis: Sensibility analysis was utilized to examine whether the results could have been influenced by a single study by removing one study at a time. We use STATA 14 software to conduct it.

Language: English.

Country(ies) involved: China.

Keywords: Meta-analysis, PD-1 inhibitor; Immune checkpoint inhibitors; PD-L1 inhibitor; geographic location.

Contributions of each author:

Author 1 - Manyu Li - Manyu Li drafted the manuscript and conducted the meta-analysis.

Author 2 - Jiannan Yao - Jiannan Yao searched for literature and extracted data.

Author 3 - Huiyun Zhang.

Author 4 - Yang Ge.

Author 5 - Guangyu An.