INPLASY

Efficacy and toxicity of immune checkpoint inhibitors combination therapy for advanced renal cell carcinoma: A systematic review and network meta-analysis

INPLASY202410078

doi: 10.37766/inplasy2024.1.0078

Received: 18 January 2024

Published: 18 January 2024

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ADMINISTRATIVE INFORMATION

Support - National Natural Science Funds of China, Grant/Award Number: 82171594.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202410078

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 January 2024 and was last updated on 18 January 2024.

INTRODUCTION

Review question / Objective Although immune checkpoint inhibitors (ICIs) show a significant overall survival advantage over standard advanced renal cell carcinoma (aRCC) therapies, tumor response to these agents remains poor. Some studies have shown that combination therapy including an ICI appears to be the best treatment; however, the overall benefit in terms of efficacy and toxicity still needs to be assessed. Thus, we performed a network meta-analysis to evaluate the differences in the efficacy of several combinations that include an ICI to provide a basis for clinical treatment selection.

Condition being studied Kidney cancer is among the 10 most common cancers in both men and women, representing 4.2% of all new cancer cases. It is estimated that approximately 81800 people will be diagnosed with kidney cancer by 2023 in the United States . Renal cell carcinoma (RCC) is the most common form of kidney cancer, accounting for 90% of all tumors. As many as 40% develop metastasis after primary surgical treatment of localized RCC. Although prognosis for patients with advanced RCC (aRCC) has improved significantly over the past decade, the vast majority of patients will ultimately die from their disease. Thus, there is an urgent need to investigate additional treatment options.

METHODS

Participant or population Patients diagnosed with advanced renal cell carcinoma.

Intervention The participants were assigned to receive pembrolizumab plus axitinib, nivolumab plus ipilimumab, avelumab plus axitinib, nivolumab

plus cabozantinib, or pembrolizumab plus lenvatinib.

Comparator Patients took sunitinib.

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

Eligibility criteria The inclusion criteria for eligible studies were as follows: (a) the study employed a randomized controlled design; (b) only one ICIs combination therapy was tested in each trial intervention; (c) aRCC had all progressed during the study; (d) primary and secondary endpoints were included; and (e) either the hazard ratio (HR) or the number of events could be extracted from the text. The exclusion criteria were as follows: (a) publications were duplicated or contained poor-quality information; (b) the study contained insufficient primary data or incomplete study data; and (c) the publications were reviews, abstracts, commentaries, letters, or case reports.

Information sources We conducted a thorough search of PubMed, EMBASE, and the Cochrane Library for articles from January 2020 up to June 2023, using a combination of the following keywords: immune checkpoint inhibitors, renal cell carcinoma, sunitinib, pembrolizumab, nivolumab, avelumab, and ipilimumab.

Main outcome(s) For each study, hazard ratios (HR) and confidence intervals (CI) of the primary endpoints were extracted, including OS and PFS, whereas for ORR, the number of patients who experienced complete response, partial response, and AEs was extracted.

Quality assessment / Risk of bias analysis The quality of the included trials was assessed using the Cochrane Collaboration tool to assess the risk of bias in randomized controlled trials.

Strategy of data synthesis Stata 16.0 and R 4.4.2 were used to analyze the data. HR, odds ratio (OR), and 95% CI were used as measures of effect size for all included studies. For indirect comparison of selected endpoints, we performed a Bayesian network meta-analysis using the GeMTC package in R. Considering that there was only one data point per intervention, no source of heterogeneity was assessed; therefore, indirect comparisons were made uniformly using a fixed-effects model.

Subgroup analysis We conducted a subgroup analysis according to age and sex to highlight any differences in survival outcomes between ICI-based combinations and sunitinib.

Sensitivity analysis If there were no differences in indirect comparisons, rank probability (for OS and PFS) or surface under the cumulative ranking (SUCRA) (for ORR, complete response, partial response, and AEs) was used to provide a posterior probability of each intervention for selected outcomes.

Country(ies) involved China.

Keywords Immune checkpoint inhibitors; Tyrosine kinase inhibitors; Advanced renal cell carcinoma; Combination therapy; Efficacy.

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