# Efficacy and Safety of PD-1/PD-L1 Inhibitors for Renal Cell Carcinoma: A Meta-Analysis Post-print

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## Abstract

Background: Renal cell carcinoma (RCC) has an insidious onset and lacks typical early clinical manifestations; most patients are diagnosed with metastasis or at an advanced stage, and radical nephrectomy yields poor efficacy. In recent years, with the widespread application of targeted therapy in tumors, postoperative recurrence and mortality rates have been significantly reduced; however, due to certain adverse reactions and complications, evidence-based support for the clinical efficacy and safety of these treatments is lacking.

Objective: To systematically evaluate the efficacy and safety of programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors in the treatment of renal cell carcinoma.

Methods: A computerized search was conducted on CNKI, Wanfang Data Knowledge Service Platform, VIP, as well as English databases including PubMed, Web of Science, Embase, Cochrane Library, and ClinicalTrials.gov, supplemented by manual retrieval, to collect randomized controlled trials (RCTs) of PD-1/PD-L1 inhibitors for renal cell carcinoma. The experimental group received PD-1/PD-L1 inhibitor therapy, while the control group received conventional treatment or placebo. The search period spanned from database inception to September 30, 2022. Two researchers independently extracted and organized data, assessed the quality of included studies according to the Cochrane Handbook 5.3 criteria, and performed meta-analysis using RevMan 5.4 software.

Results: A total of 11 studies were included, comprising 7,895 participants (3,936 in the experimental group and 3,959 in the control group). Meta-analysis results showed that the experimental group had superior overall survival (OS) and progression-free survival (PFS) compared with the control group

[HR=0.87, 95%CI (0.84, 0.90), P<0.00001; HR=0.85, 95%CI (0.78, 0.92), P<0.00001]. The objective response rate (ORR), partial response rate (PR), complete response rate (CR), and disease control rate (DCR) were higher in the experimental group than in the control group [RR=1.72, 95%CI (1.39, 2.12), P<0.00001; RR=1.56, 95%CI (1.20, 2.01), P=0.0007; RR=3.05, 95%CI (2.39, 3.09), P<0.00001; RR=1.12, 95%CI (1.05, 1.20), P=0.0005]. The stable disease rate (SD) was lower in the experimental group than in the control group [RR=0.66, 95%CI (0.62, 0.72), P<0.00001]. No statistically significant differences were observed between the experimental and control groups in disease progression rate (PD), overall adverse event rate (AEs), grade I–II adverse event rate, or grade III–V adverse event rate [RR=0.73, 95%CI (0.53, 0.99), P=0.05; RR=1.01, 95%CI (0.89, 1.04), P=0.60; RR=1.02, 95%CI (0.88, 1.17), P=0.82; RR=1.02, 95%CI (0.88, 1.19), P=0.80]. Egger's test results were all P>0.05, indicating no significant publication bias among the studies.

Conclusion: PD-1/PD-L1 inhibitors for renal cell carcinoma can significantly improve and enhance patients' OS, PFS, ORR, PR, CR, and DCR, without increasing the incidence of adverse events in terms of safety, thereby confirming the clinical superiority of PD-1/PD-L1 inhibitors in the treatment of renal cell carcinoma regarding both efficacy and safety.

## Full Text

# Efficacy and Safety of Programmed Death-1/Programmed Death-1 Ligand Inhibitors in the Treatment of Renal Cell Carcinoma: A Meta-Analysis

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### Abstract

**Background:** Renal cell carcinoma (RCC) is characterized by insidious onset and lack of early typical clinical manifestations, with most patients diagnosed at metastatic or advanced stages where radical nephrectomy demonstrates poor efficacy. While targeted therapy has been widely applied in recent years, substan-

tially reducing postoperative recurrence and mortality rates, its clinical efficacy and safety lack evidence-based support due to adverse effects and complications.

**Objective:** To systematically evaluate the efficacy and safety of programmed death-1 (PD-1)/programmed death-1 ligand (PD-L1) inhibitors in the treatment of renal cell carcinoma.

**Methods:** We conducted a comprehensive search of CNKI, Wanfang Data, VIP, PubMed, Web of Science, Embase, Cochrane Library, and Clinical Trials databases from inception to September 30, 2022, supplemented by manual searching, to identify randomized controlled trials (RCTs) of PD-1/PD-L1 inhibitors for RCC. The experimental group received PD-1/PD-L1 inhibitor therapy, while the control group received conventional treatment or placebo. Two researchers independently extracted and collated data, assessed literature quality according to Cochrane Handbook 5.3 criteria, and performed meta-analysis using RevMan 5.4 software.

**Results:** Eleven studies involving 7,895 participants were included (3,936 in the experimental group and 3,959 in the control group). Meta-analysis revealed that the experimental group demonstrated superior overall survival (OS) and progression-free survival (PFS) compared to the control group [HR=0.87, 95%CI (0.84, 0.90), P<0.00001; HR=0.85, 95%CI (0.78, 0.92), P<0.00001]. The experimental group also showed higher objective response rate (ORR), partial response rate (PR), complete response rate (CR), and disease control rate (DCR) [RR=1.72, 95%CI (1.39, 2.12), P<0.00001; RR=1.56, 95%CI (1.20, 2.01), P=0.0007; RR=3.05, 95%CI (2.39, 3.09), P<0.00001; RR=1.12, 95%CI (1.05, 1.20), P=0.0005], while stable disease rate (SD) was lower [RR=0.66, 95%CI (0.62, 0.72), P<0.00001]. No statistically significant differences were observed between groups in progressive disease rate (PD), total adverse event rate (AEs), grade I-II adverse events, or grade III-V adverse events [RR=0.73, 95%CI (0.53, 0.99), P=0.05; RR=1.01, 95%CI (0.89, 1.04), P=0.60; RR=1.02, 95%CI (0.88, 1.17), P=0.82; RR=1.02, 95%CI (0.88, 1.19), P=0.80]. Egger's test results (all P>0.05) indicated no significant publication bias.

**Conclusion:** PD-1/PD-L1 inhibitors significantly improve OS, PFS, ORR, PR, CR, and DCR in RCC patients without increasing adverse event rates, demonstrating clinical superiority in both efficacy and safety for renal cell carcinoma treatment.

**Keywords:** Carcinoma, renal cell; Programmed cell death 1 receptor; Immune checkpoint inhibitors; Efficacy; Safety; Meta-analysis

## Introduction

Renal cell carcinoma (RCC), a malignant urinary tract tumor originating from renal tubular epithelial cells, accounts for 80%-90% of kidney malignancies and represents the sixth most common cancer in men and eighth in women globally.

Its incidence increases by 1.6% annually with poor prognosis and male predominance. Radical surgery remains the primary treatment modality; however, approximately 25% of patients present with intermediate-to-advanced disease or distant metastasis at diagnosis, and 20%-50% of patients with localized RCC eventually develop metastatic disease after surgery. Metastatic RCC (mRCC) exhibits resistance to conventional chemoradiotherapy and multidrug resistance, resulting in poor postoperative outcomes with approximately 80% of patients surviving less than five years.

Recent advances in tumor immunotherapy have provided new treatment options for mRCC and advanced RCC (aRCC). Programmed death-1 (PD-1)/programmed death-1 ligand (PD-L1) inhibitors, as immune sentinel monoclonal antibodies, have been widely applied in melanoma, lung cancer, lymphoma, and renal cancer, garnering significant attention in mRCC treatment. Studies demonstrate that PD-1/PD-L1 inhibitors substantially improve clinical outcomes and prolong survival in RCC patients. International multicenter randomized controlled trials including IMmotion010, CheckMate 025, CheckMate 214, and KEYNOTE-426 have evaluated the efficacy and safety of PD-1/PD-L1 inhibitors such as atezolizumab, nivolumab, and pembrolizumab as monotherapy or combination therapy for RCC, though conclusions remain heterogeneous. This meta-analysis systematically evaluates published literature on PD-1/PD-L1 inhibitors for RCC to provide robust evidence-based guidance for immunotherapy.

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## Methods

### 1.1 Inclusion and Exclusion Criteria 1.1.1 Study Types and Participants

We included published Phase II and III randomized controlled trials (RCTs) in Chinese or English involving pathologically confirmed RCC patients, with no restrictions on age, gender, TNM stage, medical history, or medication history.

### 1.1.2 Interventions

The experimental group received PD-1/PD-L1 inhibitor therapy, while the control group received conventional treatment or placebo.

### 1.1.3 Outcome Measures

Efficacy outcomes included: (1) Overall survival (OS), defined as time from randomization to death from any cause; (2) Progression-free survival (PFS), defined as time from randomization to first disease progression or death (whichever occurred first); (3) Complete response (CR), defined as complete disappearance of all target lesions except nodal disease; (4) Partial response (PR), defined as $ $30% reduction in sum of diameters of all measurable target lesions; (5) Objective response rate (ORR), defined as proportion of patients achieving tumor reduction of predetermined magnitude for a minimum duration, including CR+PR; (6) Progressive disease rate (PD), defined as $ $20% increase in sum

of target lesion diameters or appearance of new lesions; (7) Stable disease rate (SD), defined as neither sufficient shrinkage for PR nor sufficient increase for PD; (8) Disease control rate (DCR), defined as percentage of patients achieving CR, PR, or stable disease. Safety outcomes included treatment-related adverse event rates: total adverse events (AEs), grade I-II adverse events, and grade III-V adverse events.

#### 1.1.4 Exclusion Criteria

We excluded: (1) duplicate publications, case reports, and reviews; (2) retrospective studies; (3) abstracts without results; (4) non-controlled studies; (5) non-randomized Phase II/III trials.

**1.2 Literature Search Strategy** We systematically searched CNKI, Wanfang Data, VIP, PubMed, Web of Science, Embase, Cochrane Library, and Clinical Trials databases from inception to September 30, 2022, supplemented by manual searching. We combined subject headings with free-text terms. Chinese search terms included: kidney tumor, renal cancer, renal cell carcinoma, renal adenocarcinoma, collecting duct carcinoma, tumor, cancer, malignancy, programmed cell death 1 inhibitor, programmed death 1 inhibitor, programmed death-1 ligand, immune checkpoint inhibitor, toripalimab, PD-1/PD-L1 inhibitor, nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq), durvalumab, avelumab, camrelizumab, sintilimab, tislelizumab. English search terms included: Renal Neoplasms, Kidney Cancers, Renal Cancers, Renal Cell Carcinomas, Tumor, Cancer, Malignancy, PD-1, PD-L1, Programmed Cell Death Protein 1, Programmed Cell Death Protein 1 Inhibitors, Immune Checkpoint Inhibitor, PD-L1 Inhibitors, Nivolumab, Opdivo, ONO 4538, pembrolizumab, keytruda, SCH-900475, lambrolizumab, atezolizumab, Tecentriq, MPDL3280A, durvalumab, Imfinzi, MEDI 4736, Bavencio, Avelumab, MSB0010718C, Camrelizumab, SHR-1210, sintilimab. The PubMed search strategy is detailed in .

**1.3 Literature Screening and Data Extraction** Two researchers independently screened studies according to inclusion/exclusion criteria and extracted data using a predefined form, with cross-verification. Disagreements were resolved through discussion with a third reviewer. Extracted data included: (1) study characteristics (first author, publication year); (2) participant information (sample size); (3) intervention details; (4) outcome measures (OS, PFS, ORR, PR, CR, SD, PD, DCR, AEs).

**1.4 Quality Assessment and Risk of Bias Evaluation** Two researchers assessed literature quality according to Cochrane Handbook 5.3 criteria. Publication bias was evaluated using Egger's and Begg's tests.

**1.5 Statistical Methods** We performed meta-analysis using RevMan 5.4 software. Hazard ratios (HR) and 95% confidence intervals (95%CI) assessed

associations between PD-1/PD-L1 inhibitors and OS/PFS. Relative risk (RR) and 95%CI evaluated associations with ORR, PR, CR, SD, PD, DCR, and AEs. Heterogeneity was assessed using $^2$ test and $I^2$ statistic. Fixed-effects models were used for homogeneous studies (P$ 0.1, $I^{\{2\}\$\$\ 50}\{2\}\$>50\%$). Statistical significance was set at $\alpha$=0.05.

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## Results

**2.1 Literature Screening and Selection** The initial search yielded 4,491 records. After removing 739 duplicates, 3,752 records underwent title/abstract screening, excluding 3,522 irrelevant studies, reviews, case reports, and observational studies. Full-text review of 230 articles led to exclusion of 219 studies due to design mismatch, non-randomization, non-extractable data, or retrospective design. Ultimately, 11 studies were included in the meta-analysis [Figure 1: see original paper].

**2.2 Characteristics and Quality of Included Studies** The 11 included studies comprised 7,895 patients (3,936 experimental, 3,959 control). Detailed characteristics are presented in . Risk of bias assessment is summarized in [Figure 2: see original paper] and [Figure 3: see original paper].

**2.3 Efficacy and Safety Outcomes 2.3.1 Efficacy**

**Overall Survival:** Ten studies reported OS. Heterogeneity testing showed no statistical heterogeneity (P=0.41, $I^2$=3%), warranting a fixed-effects model. Meta-analysis demonstrated superior OS in the experimental group [HR=0.87, 95%CI (0.84, 0.90), P<0.00001] [Figure 4: see original paper].

**Progression-Free Survival:** Nine studies reported PFS. Significant heterogeneity was observed ($I^2$=87%, P<0.00001), requiring a random-effects model. The experimental group showed superior PFS [HR=0.85, 95%CI (0.78, 0.92), P<0.00001] [Figure 5: see original paper].

**Objective Response Rate:** Nine studies reported ORR with substantial heterogeneity ($I^2$=89%, P<0.00001). Random-effects analysis revealed higher ORR in the experimental group [RR=1.72, 95%CI (1.39, 2.12), P<0.00001] [Figure 6: see original paper].

**Partial Response Rate:** Nine studies reported PR with high heterogeneity ($I^2$=91%, P<0.00001). The experimental group demonstrated higher PR [RR=1.56, 95%CI (1.20, 2.01), P=0.0007] [Figure 7: see original paper].

**Complete Response Rate:** Nine studies reported CR without significant heterogeneity ($I^2$=0%, P=0.74). The experimental group showed higher CR [RR=3.05, 95%CI (2.39, 3.09), P<0.00001] [Figure 8: see original paper].

**Progressive Disease Rate:** Nine studies reported PD with high heterogeneity ($I^2$=84%, P<0.00001). No significant difference was found between groups [RR=0.73, 95%CI (0.53, 0.99), P=0.05] [Figure 9: see original paper].

**Stable Disease Rate:** Seven studies reported SD without significant heterogeneity ($I^2$=43%, P=0.10). The experimental group had lower SD [RR=0.66, 95%CI (0.62, 0.72), P<0.00001] [Figure 10: see original paper].

**Disease Control Rate:** Nine studies reported DCR with substantial heterogeneity ($I^2$=77%, P<0.00001). The experimental group showed higher DCR [RR=1.12, 95%CI (1.05, 1.20), P=0.0005] [Figure 11: see original paper].

### 2.3.2 Safety

**Total Adverse Events:** Nine studies reported treatment-related AEs with high heterogeneity ($I^2$=86%, P<0.00001). No significant difference was observed between groups [RR=1.01, 95%CI (0.89, 1.04), P=0.60] [Figure 12: see original paper].

**Grade I-II Adverse Events:** Nine studies reported grade I-II AEs with high heterogeneity ($I^2$=87%, P<0.00001). No significant difference was found [RR=1.02, 95%CI (0.88, 1.17), P=0.82] [Figure 13: see original paper].

**Grade III-V Adverse Events:** Nine studies reported grade III-V AEs with high heterogeneity ($I^2$=91%, P<0.00001). No significant difference was observed [RR=1.02, 95%CI (0.88, 1.19), P=0.80] [Figure 14: see original paper].

**2.4 Publication Bias** Begg's and Egger's tests for OS showed P=0.929 and P=0.987, respectively, indicating no significant publication bias. Egger's tests for other outcomes all yielded P>0.05, suggesting minimal publication bias across studies .

**2.5 Sensitivity Analysis** Sensitivity analysis for OS and PFS demonstrated that changing effect models did not substantially alter results. The trim-and-fill method confirmed good stability of meta-analysis findings [Figure 15: see original paper].

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## Discussion

RCC ranks as the 12th most common cancer globally. Due to lack of early clinical features, 25%-75% of patients present with distant metastasis at diagnosis, missing optimal surgical windows. mRCC carries a poor prognosis with five-year survival rates below 10%. Even after radical nephrectomy, recurrence rates range from 10% in low-risk to 68% in high-risk patients. While targeted therapies have improved outcomes for mRCC and aRCC, resistance to first-line agents like sunitinib has limited efficacy.

PD-1, a member of the B7-CD28 co-stimulatory receptor family, is highly expressed on T lymphocytes, B lymphocytes, and monocytes, while PD-L1 is primarily expressed on tumor cells. Their specific binding leads to aberrant overexpression in tumor tissue. Activation of the PD-1/PD-L1 pathway reduces immune-mediated tissue damage but, when overactivated in tumors, suppresses CD4+ and CD8+ T cell proliferation and activation, promotes apoptosis, and weakens anti-tumor immunity, fostering immune tolerance and tumor progression. PD-1/PD-L1 inhibitors effectively block this pathway, enhancing T cell function.

European Society for Medical Oncology and European Association of Urology guidelines recommend PD-1/PD-L1 inhibitors (e.g., pembrolizumab) as monotherapy or combination therapy for intermediate- or high-risk resectable clear cell RCC, with CheckMate 025, CheckMate 214, and KEYNOTE-426 demonstrating survival benefits. The CheckMate 9ER study showed nivolumab plus cabozantinib achieved median OS of 37.7 months versus 34.3 months with sunitinib, with PFS doubling. IMmotion151 demonstrated improved ORR and OS with PD-1/PD-L1 inhibitors, particularly in PD-L1-positive populations, though treatment-related adverse events were more common than with sunitinib, typically affecting quality of life through gastrointestinal and dermatological toxicities.

Our meta-analysis of 11 high-quality international Phase II/III RCTs demonstrates that PD-1/PD-L1 inhibitors (atezolizumab, pembrolizumab, nivolumab, avelumab) confer significant clinical benefits in advanced RCC, improving OS, PFS, ORR, PR, CR, and DCR without increasing adverse event rates. However, substantial heterogeneity existed across studies, potentially due to: (1) large variations in sample size, population distribution, ethnicity, and tumor types; (2) differences in prior first-line chemotherapy; (3) inadequate randomization and blinding in some trials; (4) variations between monotherapy and combination therapy and among different agents; (5) patient dropout and loss to follow-up due to adverse events. Additional factors such as outcome measurement methods, geographic distribution, gender, and TNM stage may contribute, though limited data precluded stratified analysis.

**Limitations:** The relatively small number of included studies and sample sizes necessitate further validation through additional high-quality, multicenter RCTs to provide more comprehensive evidence for RCC immunotherapy.

**Conclusion:** PD-1/PD-L1 inhibitors demonstrate efficacy and safety advantages in treating advanced RCC, significantly improving survival outcomes without increasing toxicity. However, larger, high-quality multicenter RCTs are needed to strengthen these findings.

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