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*Review*

# Immunotherapeutic Innovations in Clear Cell Renal Cell Carcinoma: Current Strategies and Future Directions

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**Abstract.** *Approximatively 80% of kidney cancers globally are clear cell kidney cancers (ccRCCs), with 80% of these malignancies featuring an inactivating mutation of the Von Hippel-Lindau gene. This genetic alteration leads to the stabilization of hypoxia inducible factors 1 and 2 alpha (HIF 1 and 2α), resulting in the over-expression of target genes such as vascular endothelial growth factor (VEGF), which is crucial for angiogenesis. As a result, ccRCCs are highly vascularized and serve as models for anti-angiogenic treatments (AAT). Current AAT therapies comprise antibodies targeting VEGFs, tyrosine kinase inhibitors (TKi) (Sunitinib) that target neo-angiogenesis receptors, and competitive inhibitor receptors (Aflibercept) that trap VEGFA and PlGF. The over-expression of VEGF and related members such as VEGFC significantly influences angiogenesis, lymph-angiogenesis, and immune tolerance. This has resulted in the approval of various immune checkpoint inhibitors (known as anti-PD-1, anti-PD-L1, and anti-CTLA-4) as viable treatment options for kidney cancer. Despite these advances, ccRCC remains challenging to treat adequately. Thus, future research is imperative to better understand the biology and pathophysiology of RCC, the tumor microenvironment, and mechanisms of resistance, with the aim of developing new therapies.*

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Kidney cancer accounts for 3% of all cancers globally and is the third most common urological malignancy, following prostate and bladder cancers. The most prevalent histological subtype, renal cell carcinoma (RCC), represents over 85% of all kidney cancer cases and is notably common in developed regions. In North America and Europe, the incidence rates are 10 times higher compared to Asia or Africa. This type of cancer predominantly affects male patients between the ages of 60 and 70. Although advances in imaging protocols have improved our diagnostic capabilities, the presence of nonspecific symptoms often results in the disease being detected at a late stage.

Clear cell RCCs (ccRCCs) comprise 80% of kidney cancers and are characterized by mutations in the Von Hippel-Lindau (*VHL*) gene. These mutations result in the over-expression of vascular endothelial growth factor (VEGF), making ccRCC a paradigm for anti-angiogenic treatments (AAT).

Recent developments in cancer immunology have renewed interest in immunotherapy for cancer treatment, with the

cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) signaling pathways recognized as critical checkpoints in tumor-induced immunosuppression (1).

## The Role of the Immune System in Renal Cancer

The immune system constitutes a highly intricate network of cells, tissues, and organs designed to safeguard the host against external pathogens and the development of tumors. Its primary function lies in the capacity to identify structures that are "non-self" or have undergone alterations in infected or transformed cells. Such molecules, recognized by the immune system, are referred to as antigens. In vertebrates, the immune system is categorized into two distinct components based on the specificity of antigens and the speed of activation: innate and adaptive immunity (1, 2).

The immune system's ability to detect and eliminate tumor cells has been a subject of extensive research for many decades. Back in 1909, Paul Ehrlich postulated that the immune system could serve as a defense mechanism against neoplastic diseases. Nearly five decades later, the concept of cancer immuno-surveillance was introduced by Burnet and Thomas.

Their hypothesis supported by data from studies involving immunodeficient mice, led to a greater understanding of the human immune system's capability to surveil and respond to cancerous cells (3). Later, Schreiber and colleagues proposed a more intricate theory, suggesting that immunity has a dual role: not only in protecting the host from tumor development but also in promoting tumor growth by fostering the emergence of more aggressive tumors. This phenomenon has been described as "cancer immune editing". The process of cancer development is a multistep one, marked by the disruption of oncogenes, tumor suppression, and pro-apoptotic signals. Genetic and epigenetic changes disrupt normal cell growth, proliferation, and differentiation, resulting in tumor formation (3).

As outlined by Hanahan and Weinberg, six essential changes in cell physiology contribute to the transformation of normal cells into malignant cancer cells:

a) Self-sufficiency in growth signals: Numerous cancer cells acquire the capacity to produce their own growth factors, reducing their dependence on external triggers. b) Insensitivity to anti-growth signals: Tumor cells often disable inhibitory signals like transforming growth factor-β (TGF-β) to maintain proliferative activity. c) Limitless replicative potential: Most malignant cells up-regulate telomerase, allowing them to replicate indefinitely. d) Evading apoptosis: Cancer cells can resist programmed cell death through various mechanisms. e) Sustained angiogenesis: Tumors promote the development of new blood vessels to ensure a constant supply of oxygen and nutrients. f) Tissue invasion and metastasis: As tumors progress, cancer cells can invade surrounding tissues and spread to distant sites (4).

In healthy individuals, the bone marrow produces hematopoietic stem cells, which give rise to immature myeloid cells. Under normal conditions, these cells develop into mature immune cells in peripheral lymphoid organs. However, various pathologic conditions, including infections, trauma, inflammation, or cancer, can impede their differentiation, leading to the expansion of immature myeloid cells. As a response to various factors derived from tumors or pathogens, these immature cells can mature into myeloid-derived suppressor cells (MDSCs). These cells will produce and release factors that will inhibit immune responses (5).

In humans, it is challenging to identify MDSCs due to the lack of specific markers, making their definition vaguer compared to mice. Rodriguez *et al*. suggested CD66b as a marker for the granulocytic MDSC subpopulation in RCC patients. Although RCC triggers a robust immune response, tumors can evade immune destruction, causing a dysfunction of immune cells within the tumor (5).

A decade ago, high-dose interleukin-2 (IL-2) and interferon-gamma (IFN-γ) were the main cytokine treatments for metastatic renal cancer. However, these treatments exhibited limited success, and their associated toxicities restricted their use to select patients. Clinical research has now shifted towards alternative immunotherapies with fewer side effects, such as immune checkpoint inhibitors (5, 6). The identification of checkpoint inhibitors, including those against CTLA-4 and PD-1, has opened new possibilities for immunotherapy (5-7). CTLA-4 plays an essential role in the priming and activation of T cells, whereas PD-1 functions on effector T cells within the tumor microenvironment.

PD-1 has two ligands, PD-L1 and PD-L2, with PD-L1 being expressed widely throughout the body. Tumors exploit this by expressing PD-L1 to inhibit T cell responses, thereby avoiding immune destruction (7).

Research into PD1/PD-L1 blockade therapy has yielded promising results, with drugs like nivolumab, a well-studied anti-PD-1 antibody, demonstrating a significant response rate of 27% in RCC cases. Nivolumab restores anti-tumor activity and exerts its effects within the tumor microenvironment (8). It has also been shown to produce relatively low levels of toxicity, accompanied with durable responses.

## Treatment Update in Renal Cell Carcinoma

Systemic treatment options for advanced RCC have undergone significant advancements over the years. These range from antiangiogenic vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors to immune checkpoint inhibitors (ICIs) targeting T cell immune response, as well as mTOR inhibitors (Figure 1). Consequently, several studies have been conducted to evaluate the survival outcomes in patients that benefitted from monotherapy *versus* combined therapy strategies. According to a meta-analysis involving about 1,833

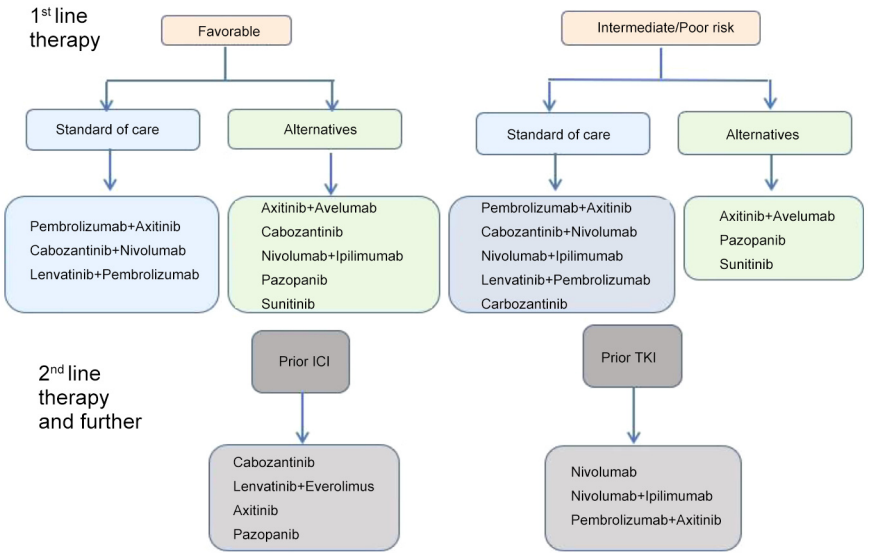


Figure 1. *Systemic treatment options in advanced renal cell carcinoma. TKI: Tyrosine kinase inhibitors; ICI: immune checkpoint inhibitors.*

patients with metastatic RCC, it was revealed that those treated with ICI-based therapy exhibited a more favorable treatment-free survival rate. Immune checkpoint inhibitors (ICI) have shown the potential to lead to sustained responses in metastatic renal cell carcinoma (mRCC). However, the optimal duration of therapy remains uncertain. Our analysis indicates that a subset of patients with mRCC who are treated with ICI-based therapy can achieve durable treatment-free survival (TFS) after discontinuation of therapy. The pooled objective response rate (ORR) was found to be 43%, with significant differences observed among patients receiving different ICI regimens. Notably, patients treated with dual ICI therapy had higher TFS rates compared to those treated with ICI plus a VEGF pathway inhibitor.

These findings underscore the necessity for further prospective clinical trials and the development of biomarkers to identify patients who can safely discontinue ICI therapy without compromising clinical outcomes. The feasibility of discontinuing ICI therapy, even in the absence of disease progression or excessive toxicity, is supported by our data. Future research should focus on identifying predictive factors that can help determine which patients can safely discontinue ICI therapy before disease progression or the occurrence of unacceptable toxicities. This approach could maximize clinical benefits while minimizing adverse effects and financial burdens (9).

Additionally, six cohorts received a combination of ICI and a VEGF pathway inhibitor. The treatment-free survival rates varied significantly at both 6 months ($p$=0.01) and 12 months ($p$<0.001) among the different subgroups of patients. The highest rates were observed in patients treated with dual ICI therapy with 57% and 50% at 6 and 12 months, respectively. In comparison, those treated with a combination of ICI and VEGF pathway inhibitor had lower survival rates of 20% and 5% at 6 and 12 months, respectively (9).

As first line systemic therapy, the combination of ICIs nivolumab and ipilimumab demonstrated higher overall survival compared to sunitinib in monotherapy (53% *vs*. 43%) and higher PFS (31% *vs*. 17% at 4 years) (10). Complete response rates were also higher in the group that received ICI, compared to the group that received VEGF pathway inhibitors (11% *vs*. 3%). 86% of the patients treated with dual ICI who achieved complete response presented a durable ongoing disease response, which was associated with fewer side effects and a better quality of life (11, 12).

Not only dual ICI showed a better therapeutic response in comparison to single-agent sunitinib, but also the combination of pembrolizumab and VEGF inhibitor axitinib demonstrated a superior overall survival (at 2 years, 74% *versus* 65%) and progression-free survival rates (38% *versus* 27%) compared to sunitinib, along with a higher complete response rate (9% *versus* 3%). However, the patients treated with the dual therapy had a higher rate of side effects compared to those that received only sunitinib (67% *versus* 62%), mainly consisting of diarrhea or hypertension (13).

While RCC has an ability to evade the immune system, developments in understanding the immune system's role in cancer development and progression have led to innovative therapies targeting immune evasion mechanisms. ICIs have become standard therapies for various cancers, including RCC. Additionally, personalized cancer vaccines, adoptive cell transfer, and other forms of immunotherapy are being

investigated to bolster the immune system's ability to target and destroy cancer cells (6).

The immune evasion strategies employed by RCC necessitate the ongoing exploration of new immunotherapeutic strategies and combination therapies that can modulate the immune response effectively to target and eliminate RCC cells. Advances in these fields may offer new hope for improved treatment outcomes for patients diagnosed with RCC.

Further research is focused towards investigating the therapeutic outcomes of combining ICIs and VEGF inhibitors, specifically nivolumab and cabozantinib. This combination exhibited a more favorable response in terms of overall survival rates at one year (86% *versus* 76%) and progression-free survival rates, with a median of 17 months *versus* 8 months when compared to using the single agent therapy, sunitinib. Moreover, the group of patients receiving the dual therapy achieved a higher complete response rate (8% *versus* 5%) and experienced a faster median time to response (2.8 *versus* 4.2 months) (14, 15).

Also, therapeutic combinations based on the association of lenvatinib and ICI (such as pembrolizumab) or mTOR inhibitors (everolimus) have shown improved progression-free survival rates compared to single agent sunitinib. Specifically, in the group treated with pembrolizumab, the median progression-free survival was 24 months *versus* 9 months with sunitinib. Similarly, in the group treated with everolimus, it was 15 months *versus* 9 months with sunitinib (16-18).

The patients that received lenvatinib and pembrolizumab also presented a longer overall survival rate and a superior rate of complete response compared to those treated with sunitinib (16% *versus* 4%), similar to the combination of lenvatinib and everolimus that showed a rate of complete response of 10% *versus* 4% for sunitinib (16).

The treatment's landscape has been dramatically revolutionized by immunotherapy for various tumors, including RCC. While RCC showed some responsiveness to immunotherapy during the era of IFNα and IL2, long-term clinical benefits were observed only in a few patients. However, recent progress in our understanding of key tumor drivers, as well as the role of angiogenesis and the tumor microenvironment have greatly enhanced drug development and improved patient's outcomes. Today, the standard care includes the combination of anti-angiogenic agents and ICIs. Despite these achievements, there are still challenges to address, including selecting the appropriate patients for immunotherapy combinations, managing resistance development, and optimizing the sequencing of different therapies.

## Predictive Biomarkers and Patient Selection

In the era of personalized medicine, identifying predictive biomarkers has become crucial to select appropriate patients who are likely to benefit from immunotherapies (19-21). 1) PD-L1 expression: The investigation of PD-L1 expression on tumor cells as a predictive biomarker to identify patients likely to respond to ICIs is ongoing. Nevertheless, its role remains controversial due to variability in assessment methods and its fluctuating expression levels. 2) Tumor mutational burden (TMB): A high TMB has been correlated with increased responsiveness to immunotherapy in various cancers, including RCC, by providing more neoantigens for immune recognition. 3) Gene expression profiling: Assessing the expression of genes associated with immune activation and suppression can help predict responses to immunotherapy and guide therapeutic decisions. 4) Microsatellite instability (MSI): Although more prevalent in other cancers, MSI-high tumors in RCC may also benefit from immunotherapy due to enhanced immunogenicity. 5) Integration of multiple biomarkers: Combining multiple biomarkers can improve predictive accuracy, helping clinicians tailor treatment strategies based on individual patient profiles. 6) Liquid biopsy: This is emerging as a non-invasive method to identify biomarkers such as circulating tumor DNA (ctDNA) that could predict response to immunotherapy (22).

## Optimizing Therapeutic Outcomes

Clinicians integrate the predictive information from biomarkers with clinical variables such as performance status, comorbidities, and patient preferences to determine the most suitable therapeutic approach for each patient. This patient-centered approach aims to optimize therapeutic outcomes by maximizing efficacy, while minimizing toxicity, thus enhancing the overall quality of life for patients with RCC.

In conclusion, enhancing the understanding of immune evasion mechanisms by RCC and the development of reliable predictive biomarkers are pivotal in advancing the field of immunotherapy for RCC, leading to more personalized and effective treatment strategies.

## Conclusion

Systemic treatment options for advanced RCC have significantly evolved over the years. The use of checkpoint inhibitors, both as monotherapy and in combination with other ICIs has been associated with a longer overall survival. Additionally, the combination of ICIs with VEGF inhibitors has also demonstrated a superior overall survival. Safety profiles emphasize the importance of selecting the appropriate drug and dosage for each patient (20).

## Conflicts of Interest

The Authors declare no competing interests in relation to this study.

## Authors' Contributions

Conceptualization: AZ.; Data curation: S.C., D.C.B., and B.H.; Formal analysis: T.I. and M.S.; Supervision: R.A.; Writing –

original draft: A.Z., D.S.; Writing – review & editing: R.A.; All Authors read and approved the final manuscript.

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