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Review

Application of Immune Checkpoint Inhibitors in the Treatment of Renal Cell Carcinoma: Current Status, Challenges, and Future Directions

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Abstract

In recent years, immune checkpoint inhibitors (ICI) have revolutionized the treatment landscape of renal cell carcinoma (RCC), significantly enhanced patient outcomes and expanded therapeutic options beyond traditional surgical and targeted approaches. In this review, we provide a comprehensive review of the current applications of ICI in RCC therapy, elucidating their mechanisms of action, clinical efficacy across both clear cell and non-clear cell subtypes, and safety profiles. We compare the effectiveness of monotherapy versus combination therapies, demonstrating how synergistic approaches can improve efficacy and durability of responses. Furthermore, we explore the integration of multi-omics technologies, such as single-cell RNA sequencing and spatial transcriptomics, which are pivotal in predicting ICI response and addressing resistance mechanisms. Our discussion also addresses the critical challenges in RCC immunotherapy, including primary and acquired resistance, economic and ethical barriers, and the management of immune-related adverse events. By synthesizing current research and clinical findings, this review aims to provide valuable insights for optimizing RCC immunotherapy, fostering the development of more effective and individualized treatment protocols, and ultimately improving patient survival and quality of life.

Keywords

Immune checkpoint inhibitors, renal cell carcinoma, treatment status, challenges, future directions

INTRODUCTION

Renal cell carcinoma (RCC) represents about 2-3% of all adult malignancies worldwide, with its incidence steadily increasing in recent decades. This rise is particularly evident in developed nations, where lifestyle factors such as obesity, hypertension, and smoking have contributed to a growing disease burden [1,2]. RCC is primarily diagnosed in adults, with an average age of 64 years, and is notably more common in men, with a male-to-female ratio of approximately 2:1. The disease is often asymptomatic during its early stages, leading to delayed diagnoses and poor prognosis once metastasis occurs. For patients with metastatic RCC, the five-year survival rate remains dismal at around 12% [3–5].

Risk factors for RCC include genetic predispositions (such as mutations in the von Hippel-Lindau gene), environmental exposures like smoking, and comorbid conditions including obesity and chronic kidney disease[6,7]. In addition to these, emerging evidence suggests that the gut microbiome and immune system dysregulation may play critical roles in RCC pathogenesis and treatment responses [8]. These complexities underscore the urgent need for better prevention, early detection, and therapeutic strategies to improve patient outcomes.

Traditional treatment for RCC has relied heavily on surgical resection, such as radical or partial nephrectomy, in conjunction with adjuvant therapies, including targeted agents and immunotherapies. While targeted therapies like tyrosine kinase inhibitors (TKIs) and VEGF inhibitors have improved survival in advanced RCC, these treatments are frequently limited by tumor heterogeneity and the inevitable development of therapeutic resistance[9,10]. Furthermore, despite initial responses, long-term efficacy remains limited, underscoring the need for novel and more durable treatment strategies.

In recent years, immune checkpoint inhibitors (ICI) have emerged as a transformative approach in the treatment of RCC. ICI, including anti-PD-1, anti-PD-L1, and anti-CTLA-4 monoclonal antibodies, work by blocking the immune checkpoint pathways that tumors exploit to evade immune surveillance. These therapies restore and enhance the immune system’s ability to recognize and attack tumor cells, offering substantial improvements in overall survival, especially in patients with advanced clear cell RCC (ccRCC) [11,12]. For instance, combination therapies such as nivolumab with ipilimumab or pembrolizumab with axitinib have demonstrated superior efficacy compared to traditional therapies and are now part of first-line treatment protocols for metastatic ccRCC [13].

However, while ICI have been highly effective in ccRCC, the response in non-clear cell RCC (nccRCC) is more variable and often suboptimal. NccRCC encompasses a heterogeneous group of tumors, including papillary, chromophobe, and unclassified subtypes, which exhibit distinct molecular characteristics and immune microenvironments[14]. As a result, the efficacy of ICI in nccRCC has been less predictable, with response rates varying widely depending on the subtype and the molecular alterations present[15]. This variability in treatment response highlights the importance of understanding the tumor's genetic and immune landscape to identify optimal therapeutic strategies for different RCC subtypes.

The integration of ICI into clinical practice represents a paradigm shift in the management of advanced RCC, yet challenges remain. The mechanisms of resistance to immunotherapy, including tumor-induced immune suppression and the heterogeneous nature of RCC, complicate the treatment landscape[16]. Further research is needed to better understand these mechanisms and to develop strategies to overcome resistance. Additionally, identifying reliable biomarkers that can predict patient response to ICI will be crucial for the optimization of immunotherapy in RCC, particularly for nccRCC.

In this review, we aim to provide a comprehensive overview of the current advances in immunotherapy for RCC, focusing on both ccRCC and nccRCC. We will explore the molecular mechanisms underlying the success of ICI in ccRCC, the challenges faced in treating nccRCC, and the emerging strategies to overcome treatment resistance. Finally, we will discuss future directions in RCC immunotherapy, including combination therapies, personalized approaches, and novel omics discovery, which are essential to improving the prognosis of patients with this deadly disease(Figure 1).

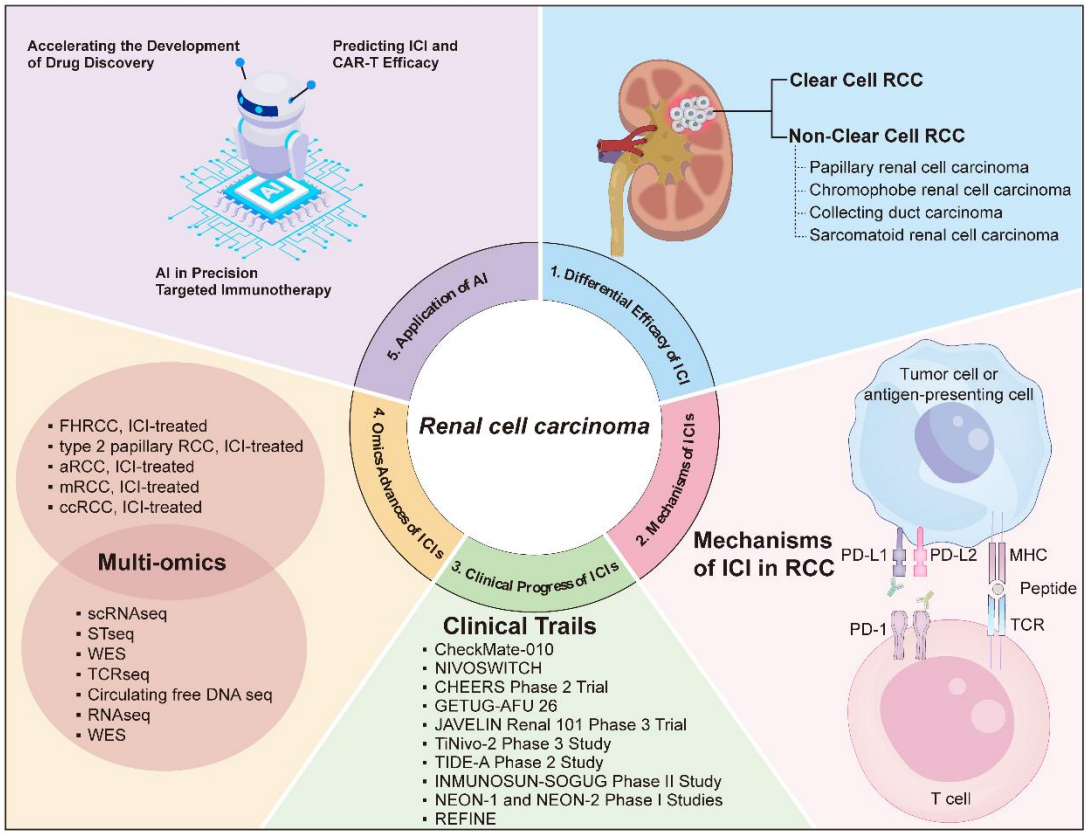


Figure 1. Schematic overview of immune checkpoint inhibitor (ICI) therapeutic applications in renal cell carcinoma (RCC).

Differential Efficacy of ICI in Clear Cell and Non-Clear Cell RCC

Renal cell carcinoma (RCC) is primarily classified into two subtypes: clear cell renal cell carcinoma (ccRCC) and non-clear cell renal cell carcinoma (nccRCC)[17]. These subtypes differ significantly in their pathological features, clinical presentation, and prognosis. CcRCC is the most common subtype, accounting for 70%-80% of all RCC cases[18], while nccRCC, which is highly heterogeneous, accounts for about 20% of RCC cases (papillary RCC accounts for 10-15%, chromophobe RCC for 4-5%, unclassified RCC for 4-6%, collecting duct carcinoma for less than 1%, and Xp11.2 translocation RCC is rare) [19,20].

In recent years, immune checkpoint inhibitors (ICI) have emerged as a major advancement in the treatment of ccRCC, with these agents becoming integral to the management of advanced or metastatic disease[21]. ICI, which target immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4, enhance the immune system's ability to recognize and attack tumor cells, leading to significant improvements in survival rates and overall patient quality of life[22]. In clinical practice, tyrosine kinase inhibitors (TKIs), such as Sunitinib, Axitinib, Pazopanib, and Cabozantinib, to enhance therapeutic outcomes and maximize treatment efficacy. For instance, the FDA has approved the combination of pembrolizumab with axitinib and nivolumab with cabozantinib as first-line therapies for advanced or metastatic ccRCC[23].

The efficacy of ICI varies significantly across different molecular subtypes of RCC. ccRCC has shown a better response to ICI, exhibiting higher sensitivity and improved clinical outcomes compared to non-clear cell subtypes[24]. Numerous studies have demonstrated that ccRCC patients derive substantial benefits from PD-1 inhibitors such as Nivolumab, with marked improvements in survival and disease progression[25]. In contrast, nccRCC patients tend to have more limited responses, with single-agent ICI showing response rates of up to 27% in both first- and second-line treatments[18]. However, combination therapies generally offer better outcomes compared to monotherapy in this group. In addition, the application of ICI in nccRCC remains more complex and less defined than in ccRCC. Recent research highlights the need for more personalized treatment strategies for nccRCC, such as targeting specific molecular pathways

like c-MET in papillary RCC, to improve therapeutic efficacy[26]. Despite some promising results, nccRCC still requires more extensive investigation to identify predictive biomarkers and optimize treatment regimens.

Thus, while ICI have demonstrated significant efficacy in ccRCC, their application in nccRCC remains less predictable and necessitates further exploration to develop tailored therapeutic approaches. Understanding these molecular and clinical differences is crucial for improving treatment outcomes in all RCC patients. Future research should focus on enhancing our understanding of the molecular mechanisms underlying the heterogeneous responses to ICI in nccRCC, as well as developing more effective treatment combinations. These efforts will be crucial in improving treatment outcomes and survival rates for patients with nccRCC.

Immune Checkpoints and the Tumor Microenvironment: Mechanisms and Clinical Implications

Mechanisms of Immune Checkpoint Inhibitors (ICI)

Immune checkpoint inhibitors (ICI) have revolutionized cancer immunotherapy by enhancing the immune system's capacity to recognize and eliminate tumor cells. These therapies primarily target critical immune checkpoints such as PD-1/PD-L1 and CTLA-4, which play essential roles in immune regulation and maintaining self-tolerance. By blocking these inhibitory pathways, ICIs restore T cell activity and promote anti-tumor immune responses, leading to significant improvements in patient outcomes. Despite the success of targeting PD-1/PD-L1 and CTLA-4, challenges such as primary and acquired resistance have emerged, underscoring the need for additional therapeutic targets. Consequently, several novel immune checkpoints, including LAG-3 (lymphocyte activation gene-3) and TIGIT (T cell immunoreceptor with Ig and ITIM domains) [27,28], are being actively investigated. These molecules, often co-expressed with PD-1 on exhausted T cells, contribute to immune suppression within the tumor microenvironment (TME) and represent promising candidates for combination therapies[29,30]. Advancements in immunotherapy have thus identified these and other novel checkpoint pathways as pivotal in regulating immune responses in RCC. Targeting these pathways not only offers new strategies to overcome resistance to conventional ICIs but also enhances the overall therapeutic efficacy, providing new hope for improving the prognosis of renal cell carcinoma patients(Figure 2).

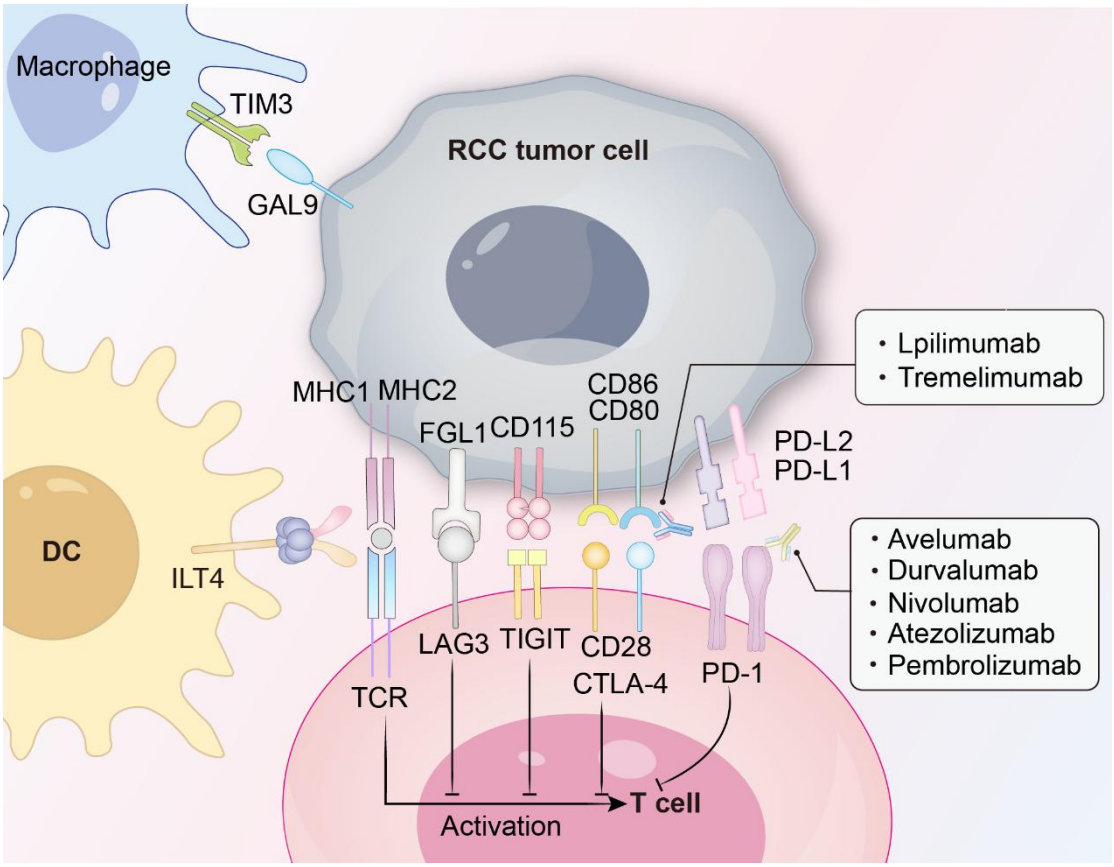


Figure 2. Mechanisms of ICI in RCC.

The signaling of immune checkpoint inhibitors (ICIs) is intricately regulated through interactions among various cells, including

histocompatibility complex (MHC) glycoproteins, engaging the T cell receptor (TCR). Key inhibitory interactions occur as PD-L1/2, CD80/CD86, CD115, and FGL1 on RCC tumor cells bind with PD-1, CD28/CTLA-4, TIGIT, and LAG3 on T cells, respectively. Additionally, RCC tumor cell-expressed GAL-9 and MHC1 interact with TIM3 on macrophages and ILT4 on dendritic cells, modulating immune responses. By blocking these inhibitory pathways, ICIs restore T cell function, enhance tumor cell recognition, and bolster anti-tumor immunity.

PD-1/PD-L1 Pathway

The PD-1 (programmed cell death protein 1) receptor is expressed on activated T cells, and its ligand, PD-L1 (programmed death-ligand 1), is often overexpressed on tumor cells. The PD-1/PD-L1 interaction inhibits T cell activation, promoting immune tolerance and allowing tumor cells to escape immune surveillance. By blocking this pathway with anti-PD-1 or anti-PD-L1 antibodies, such as nivolumab and pembrolizumab, T cell cytotoxicity is restored, enabling the immune system to target and kill tumor cells. This approach has demonstrated significant efficacy in several cancers, including melanoma, non-small cell lung cancer, and RCC (renal cell carcinoma) [31,32].

CTLA-4 Pathway

CTLA-4 (cytotoxic T lymphocyte-associated protein 4) is another critical immune checkpoint receptor that downregulates immune responses. CTLA-4 competes with CD28 for binding to B7 molecules on antigen-presenting cells, thus inhibiting T cell activation. Blockade of CTLA-4 with antibodies such as ipilimumab enhances T cell activation and proliferation, amplifying the immune response against tumors. However, this activation can also lead to immune-related adverse events (irAEs), highlighting the need for careful patient monitoring during treatment[27,33].

LAG3 Pathway

Lymphocyte Activation Gene 3 (LAG3) is an inhibitory receptor structurally similar to CD4 and is highly expressed on exhausted T cells and other immune cells. LAG3 downregulates immune responses by interacting with its ligands, thereby inhibiting T cell proliferation and function [34]. In melanoma, the combination of anti-LAG3 antibody relatlimab with anti-PD-1 nivolumab has demonstrated improved progression-free survival (PFS) compared to nivolumab alone, leading to FDA approval for advanced melanoma treatment[35,36]. In RCC, studies have shown that LAG3 expression is generally lower at metastatic sites compared to primary tumors but is associated with better responses to immunotherapy and improved survival outcomes in high-risk patients [37]. Ongoing trials are evaluating various determine their efficacy and safety in advanced RCC, aiming to enhance response rates and overcome resistance [37]

TIGIT Pathway

T Cell Immunoglobulin and ITIM Domain (TIGIT) is an inhibitory receptor expressed on various lymphocytes, including T cells and natural killer (NK) cells. TIGIT competitively binds to the immune activator receptor CD226 (DNAM-1) for ligands such as CD155 and CD112, which are nectin receptors that enhance T and NK cell activity [38]. By inhibiting CD226-mediated activation, TIGIT dampens the immune response, facilitating tumor immune evasion. Johnston et al. have identified a specific signature associated with TIGIT and PD-1 in tumor-infiltrating T cells, highlighting its role in immune suppression within the TME [39]. In clear cell RCC (ccRCC), TIGIT is predominantly expressed in tumor tissues compared to adjacent normal tissues, making it a potential target for combination therapies aimed at enhancing ICI efficacy [40]. Ongoing clinical trials are evaluating TIGIT inhibitors in combination with PD-1/PD-L1 blockers to assess their synergistic potential in improving patient outcomes [41].

ILT4 Pathway

Immunoglobulin-like Transcript 4 (ILT4) is an inhibitory receptor predominantly expressed on innate immune cells, including macrophages, monocytes, and dendritic cells. ILT4 interacts with major histocompatibility complex (MHC) class I and human leukocyte antigens (HLAs), modulating immune cell activation and promoting an immunosuppressive TME [42]. Overexpression of ILT4 has been observed in both hematologic and solid tumors, including RCC, where it contributes to tumor progression and metastasis by inhibiting anti-tumor immune responses[43]. Targeting ILT4 with monoclonal antibodies, such as MK-4830, either as monotherapy or in combination with pembrolizumab, has shown promising antitumor activity in patients with advanced solid tumors, including those with prior ICI resistance, while maintaining a favorable safety profile [44].

TIM-3 Pathway

T Cell Immunoglobulin and Mucin Domain 3 (TIM-3) is an

type 17 T helper cells (Th17), monocytes, and macrophages. TIM-3 interacts with its ligand galectin-9 (Gal-9), leading to the depletion of Th1 cells and negative regulation of immune responses, thereby promoting immune tolerance [45,46]. Overexpression of TIM-3 has been linked to poor prognosis in various cancers, including hepatocellular carcinoma and RCC [47,48]. In ccRCC, TIM-3 expression is higher in tumor tissues compared to adjacent normal tissues, and its knockdown inhibits RCC cell proliferation and invasion. Targeting TIM-3 with specific inhibitors could restore T cell function and enhance the efficacy of existing ICIs. Research is ongoing to develop TIM-3 inhibitors and evaluate their potential in combination with other ICIs to improve therapeutic outcomes in RCC patients [47,48].

Impact of the Tumor Microenvironment on ICI Efficacy

While immune checkpoint inhibitors have shown remarkable clinical success, their efficacy can be influenced by the tumor microenvironment (TME), which plays a pivotal role in regulating immune responses. The TME consists of various components, including immune cells, stromal cells, blood vessels, and signaling molecules, which collectively contribute to the tumor's ability to evade immune detection.

Tumor-Infiltrating Lymphocytes (TILs)

Tumor-infiltrating lymphocytes (TILs), especially CD8+ cytotoxic T cells, are considered key players in the anti-tumor immune response. A high density of TILs in the tumor is often associated with better prognosis and more favorable responses to ICI[49]. For instance, in RCC and other cancers, the presence of CD8+ T cells within the tumor correlates with enhanced tumor control and improved survival[50]. However, the immune landscape within tumors is highly dynamic and can vary widely across different cancer types and individual patients.

Immunosuppressive Cells in the TME

The TME is not only composed of immune-activating cells but also includes immune-suppressive populations that hinder effective anti-tumor immunity. Regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) are among the major immunosuppressive cell types in the TME. Tregs, in particular, inhibit T cell activation and promote immune tolerance, limiting the efficacy of ICI[51]. Studies have shown that high levels of Tregs within the tumor microenvironment can be associated with resistance to ICI and poorer clinical outcomes [52]. Similarly, MDSCs secrete immunosuppressive cytokines, further dampening T cell activity and contributing to immune evasion[53].

Fibroblasts and Vascular Architecture in the TME

The specific components of the TME, such as myofibroblast-like cancer-associated fibroblasts (myCAFs), fibroblasts, and aberrant vascular structures, play a crucial role in influencing immune cell infiltration and activity within RCC[54]. myCAFs may form physical and biochemical barriers through close interactions with mesenchymal tumor cells, thereby restricting immune cell infiltration and fostering immunosuppression[54–56]. Concurrently, RCC cells secrete extracellular vesicles (EVs) containing circEHD2, which activate fibroblasts and transform them into cancer-associated fibroblasts (CAFs), promoting tumor metastasis[54–56]. CAFs contribute to the immunosuppressive TME by secreting pro-inflammatory cytokines, such as IL-6, and guiding plasma cell migration via the CXCL12/CXCR4 axis[54–56]. Aberrant vascular structures create hypoxic conditions that impede immune cell function, whereas high endothelial venules (HEVs) facilitate the infiltration of T and B cells, supporting the formation and function of TLS [54–56]. Targeting myCAFs and CAFs, for instance by inhibiting TGF-β or IL-6 signaling pathways, or normalizing vasculature through anti-angiogenic therapy, such as VEGF inhibitors, can improve immune cell infiltration and activity, thereby enhancing the efficacy of ICIs [54–56]. These strategies provide new insights and pivotal directions for developing combinatorial therapies to improve therapeutic responses in RCC patients. [54]

Immune Evasion and Resistance Mechanisms

Tumor cells can also evade immune detection through a variety of mechanisms, including the secretion of immunosuppressive cytokines and the expression of immune checkpoint ligands such as PD-L1[57]. Moreover, the presence of fibrosis, altered vasculature, and metabolic stress in the TME can hinder the infiltration of immune cells into the tumor. These factors collectively create a "cold" or non-inflamed tumor environment, in which the immune system is less able to recognize and attack tumor cells. Consequently, therapies targeting immune checkpoints may have limited efficacy in such tumors [57].

Overcoming Immune Resistance: New Strategies and Future Directions

Given the complexity of the TME and its impact on immune checkpoint inhibition, there is increasing interest in strategies

strategies include: (1) Combination Therapies: Combining ICI with other treatment modalities, such as targeted therapies (e.g., tyrosine kinase inhibitors) or anti-angiogenic agents, has shown promise in improving treatment outcomes by modulating the TME and enhancing immune responses [13]; (2) Modulation of the TME: Approaches aimed at "reprogramming" the TME, such as targeting immunosuppressive cells like Tregs or MDSCs, may enhance the efficacy of ICI. Other strategies involve improving immune cell infiltration into tumors through the modulation of the tumor vasculature or the use of oncolytic viruses to directly target and "inflame" the tumor[58,59]: (3) Biomarker Discovery: Identifying biomarkers that can predict the response to ICI is critical for personalizing immunotherapy. These biomarkers may include the presence of specific immune cell populations in the TME, tumor mutational burden (TMB), and PD-L1 expression levels [60].

Summary of ICI and TME Effects

The mechanisms of immune checkpoint inhibition are complex and heavily influenced by the tumor microenvironment. While PD-1/PD-L1 and CTLA-4 blockade have revolutionized cancer treatment, the TME presents both challenges and opportunities in enhancing the efficacy of ICI. Understanding the interactions between immune cells and tumor cells within the TME is crucial for optimizing immunotherapy and overcoming resistance. Future research should focus on combination strategies, TME modulation, and the identification of predictive biomarkers to improve patient outcomes and expand the benefits of immune checkpoint inhibition across a broader range of cancers.

Clinical Research Progress: Monotherapy vs Combination Therapy in Renal Cell Carcinoma

Unique Advantages of Immunotherapy: Durability and Systemic Effects

Immunotherapy, particularly immune checkpoint inhibitors (ICI), has ushered in a new era in the treatment of advanced renal cell carcinoma (RCC). By harnessing the power of the patient's immune system, ICI block the inhibitory checkpoints that tumor cells exploit to evade immune surveillance. These therapies have not only provided significant survival benefits but have also introduced a more durable, systemic approach to cancer treatment compared to traditional methods. However, while immunotherapy presents unique advantages, it also introduces challenges that must be carefully managed to optimize outcomes[61–65].

One of the most compelling features of immunotherapy is its ability to induce long-lasting antitumor effects. Unlike traditional therapies, which often target specific tumor characteristics, ICI activate the immune system more broadly, enabling it to recognize and attack both the primary tumor and metastatic lesions—even those that may not express the same antigens. This is particularly beneficial in cancers with high antigenic variation, such as RCC, where tumor cells may escape detection by conventional therapies[61–65].

The advantages of immunotherapy could be more clearly quantified by examining the response rates and durability of clinical outcomes observed in RCC patients treated with ICI. For instance, single-agent CTLA4 blockade demonstrated modest response rates of 12.5% in high-dose cohorts and 5% in low-dose cohorts, with limited durability and significant toxicity [66]. In contrast, PD1 blockade, such as nivolumab, achieved higher objective response rates ranging from 20% to 27% in phase II trials, with some patients experiencing durable responses [67–69]. Pembrolizumab, another PD1 inhibitor, further improved response rates to 36% in advanced RCC [67]. Notably, combination therapies, such as nivolumab plus ipilimumab, significantly enhanced response rates to 42% in the CheckMate 214 trial [13], while combinations of PD1/PDL1 inhibitors with VEGF TKIs, such as avelumab plus axitinib and pembrolizumab plus axitinib, achieved even higher response rates of 55.2% and 59.3%, respectively[70,71]. These findings highlight the potential of immunotherapy to improve clinical outcomes, particularly when used in combination with other targeted therapies. However, the advantages of immunotherapy could be more clearly quantified by further investigating biomarkers of response, long-term survival benefits, and the mechanisms underlying resistance, which would enable the development of more effective and personalized treatment strategies.

In summary, the unique advantages of ICI lie in their ability to mobilize and enhance the patient's immune response, leading to durable and systemic antitumor effects, which are critical in the ongoing fight against cancer. Recent clinical trials of ICI in RCC are presented in **Table 1**.

Table 1. Recent Clinical Trials of ICI-Based Therapies in RCC.

Trial name	Regimens	Reported outcomes	OS HR	PFS HR	ORR (ICI arm)	FDA or EMA approval	Refs
CheckMate-010	Nivolumab	Improved OS, PFS, ORR	0.4	\	\	\	72
NIVOSWITCH; AIO-NZK-0116ass	Nivolumab versus Tyrosine Kinase Inhibitors (Sunitinib or Pazopanib)	Worse PFS (HR: 2.57); lower ORR compared to TKI; immature OS data; no QoL improvement.	Not mature	2.57 （Nivolumab: TKI）	20.0% for nivolumab; 52.2% for TKI.	\	74
CHEERS Phase 2 Trial	Control: Standard of care anti–PD-1/PD-L1 ICI monotherapy Experimental: ICI monotherapy + SBRT (3 × 8 Gy) to max. 3 lesions, pre-second ICI cycle	Higher OS, PFS, and ORR (Experimental arm)	0.82	0.95	Control: 22%; Experimental: 27%.	\	83
Body Mass Index, Sarcopenia, and Their Variations in Predicting Outcomes for mRCC Patients	Nivolumab	Higher BMI and weight gain correlated with better OS and response rates;	\	\	ORR increased in patients with higher BMI.	Yes	77

		sarcopenia linked to shorter OS					
GETUG-AFU 26 NIVOREN Multicenter Phase II Study	Nivolumab	Reduced OS, PFS, ORR with PPI use compared to non-PPI users.	1.52	1.38	PPI users: 12.2%; Non-PPI users: 20.3%	Yes	75
Pooled Analysis of 23 Clinical Trials on irAEs in Cancer Patients Treated with ICI	Nivolumab + Ipilimumab, Pembrolizumab + Anti–CTLA-4, Anti–PD-1/PD-L1 + Anti–CTLA-4	PMT-O of all-grade irAEs ranged from 2.2 to 14.8 weeks; PMT-R ranged from 0.1 to 54.3 weeks.	\	\	\	\	163
GETUG-AFU26-NIVOREN Multicentre Phase II Study	Nivolumab	Reduced OS, PFS, ORR in patients with BM compared to those without BM.	\	\	14.8% in patients with BM; 23.3% in patients without BM	Yes	76
JAVELIN Renal 101 Phase 3 Trial	Avelumab plus Axitinib versus Sunitinib	Improved OS, PFS, ORR (with Prior CN) No significant difference in OS, PFS, ORR between treatment arms	0.59(with Prior CN), 0.86(Without Prior CN)	0.79(with Prior CN), 1.15(Without Prior CN)	55.4% (with Prior CN), 36.4% (Without Prior CN)	Yes(first-line)	80

		(without Prior CN)					
TiNivo-2 Phase 3 Study	Tivozanib + Nivolumab versus Tivozanib	No significant improvement in OS, PFS, or ORR	1.00	1.10	Combination: 19.3%; Monotherapy: 19.8%	Yes	82
TIDE-A Phase 2 Study	Avelumab + Axitinib (intermittent)	Improved PFS, ORR	\	\	76% (12% complete response, 64% partial response)	Yes	81
INMUNOSUN-SOGUG Phase II Study	Sunitinib monotherapy	Improved OS, PFS	\	\	19%	Yes	164
NEON-1 and NEON-2 Phase I Studies	Davoceticept ± Pembrolizumab	Clinical benefit; safety concerns	\	\	\	\	84
REFINE	Extended interval ICI administration	pending	\	\	\	Not applicable; study ongoing	85
Characteristics of Lung Cancer Patients in Practice vs RCT Eligibility	TKIs versus ICI	Reduced OS in ineligible patients	\	\	\	Not applicable; study is observational	165

Abbreviation: ccRCC: Clear Cell Renal Cell Carcinoma; RCC: Renal Cell Carcinoma; FHRCC: Fumarate Hydratase-Deficient Renal Cell Carcinoma; aRCC: Advanced Renal Cell Carcinoma; mRCC: Metastatic Renal Cell Carcinoma; ICI: Immune Checkpoint Inhibitor; PMT-O: Median Time to Onset; PMT-R: Median Time to Resolution; irAEs: Immune-Related Adverse Events; ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; HR: Hazard Ratio; QoL: Quality of Life; TKI: Tyrosine Kinase Inhibitor; CN: Cytoreductive Nephrectomy; PPI: Proton Pump Inhibitor; BMI: Body Mass Index; BM: Bone Metastases.

Monotherapy with Immune Checkpoint Inhibitors

Monotherapy with PD-1 inhibitors, particularly nivolumab, has shown promising results in advanced RCC[72]. The

CheckMate-010 trial demonstrated that nivolumab, a PD-1 inhibitor, significantly improved overall survival (OS) compared to conventional therapies, reinforcing its potential as a monotherapy option for RCC[72]. Moreover, nivolumab's favorable safety profile—associated with fewer severe adverse events compared to chemotherapy—makes it a compelling treatment choice, especially for patients who have previously undergone systemic treatments[73].

However, while nivolumab offers improvements in OS, its progression-free survival (PFS) and objective response rate (ORR) were lower in the NIVOSWITCH trial, which compared nivolumab with TKIs like sunitinib or pazopanib[74]. This trial highlighted certain limitations of nivolumab, particularly for patient populations without prior cytoreductive nephrectomy (CN), where nivolumab demonstrated worse PFS and lower ORR compared to TKIs. Additionally, findings from the GETUG-AFU26-NIVOREN Phase II study revealed that concomitant use of proton pump inhibitors (PPIs) reduced the efficacy of nivolumab, leading to decreased OS, PFS, and ORR in PPI users compared to non-users[75].

Patients with bone metastases (BM) also showed worse outcomes with nivolumab monotherapy, as evidenced by the GETUG-AFU26-NIVOREN study, which reported lower ORR and poorer clinical outcomes for these individuals[76]. Furthermore, BMI and sarcopenia were found to influence outcomes, with higher BMI and weight gain correlating with better results, whereas sarcopenia was associated with shorter OS[77]. These findings emphasize the importance of considering patient-specific factors, such as metabolic status and metastatic burden, when evaluating the suitability of nivolumab monotherapy.

Combination Therapy: Enhancing Efficacy in RCC

While monotherapy with PD-1 inhibitors like nivolumab has shown clinical benefits, combination therapies have demonstrated superior outcomes in certain patient populations. Notably, the combination of Nivolumab and Ipilimumab has shown superior efficacy, particularly in high-risk patient populations. Clinical trials have reported enhanced objective response rates (ORR) and progression-free survival (PFS) when using this combination compared to monotherapy options[78]. Moreover, combining ICI with targeted therapies, such as Pembrolizumab with Axitinib, has emerged as a first-line treatment strategy for advanced RCC, demonstrating significant improvements in OS and PFS over traditional therapies like Sunitinib[79].

The JAVELIN Renal 101 trial investigated the combination of avelumab (a PD-L1 inhibitor) and axitinib (a TKI) in RCC treatment, showing significant improvements in OS, PFS, and ORR compared to sunitinib[80]. This combination approach, particularly beneficial for patients with prior cytoreductive nephrectomy (CN), is now being used as a first-line treatment for advanced RCC. The combination's success underscores the value of targeting both the immune system and tumor growth pathways simultaneously.

Similarly, the TIDE-A Phase 2 study explored intermittent avelumab and axitinib administration, achieving a 12% complete response rate and a 64% partial response rate[81]. These promising results suggest that intermittent combination therapy may offer a durable and robust response for advanced RCC patients[81]. In contrast, the TiNivo-2 trial evaluated the combination of tivozanib (another TKI) with or without nivolumab, finding no significant improvements in OS, PFS, or ORR between the combination and monotherapy arms[82]. This highlights that not all combinations necessarily provide additive benefits, and further research is needed to identify the most effective regimens.

The CHEERS Phase 2 Trial investigated the addition of stereotactic body radiotherapy (SBRT) to immune checkpoint inhibitors[83]. The results showed that the combination of SBRT and ICI significantly improved OS, PFS, and ORR compared to ICI monotherapy, highlighting the potential of combining localized therapies like radiotherapy with systemic immune treatments for enhanced efficacy[83].

Emerging Therapies and Ongoing Trials

In addition to PD-1 and PD-L1 inhibitors, novel immune checkpoint targets are being explored in clinical trials. The NEON-1 and NEON-2 trials assessed the safety and efficacy of davoceticept, a dual PD-L1/CTLA-4 inhibitor, alone or in combination with pembrolizumab[84]. Although early results show potential clinical benefits, the trials also raised

significant safety concerns that need further investigation. Another ongoing trial, the REFINE trial, is investigating the impact of extended interval immune checkpoint inhibition, with results pending. These trials represent the next frontier in RCC treatment, aiming to refine therapeutic schedules and identify new combinations that maximize efficacy while minimizing toxicity[85].

Safety and Tolerability: Managing Immune-Related Adverse Events

While ICI have significantly improved survival in patients with advanced RCC, their use is also associated with a unique set of immune-related adverse events (irAEs). These can include dermatological issues such as skin rashes, endocrine dysfunctions like thyroiditis, and gastrointestinal disturbances. Common irAEs include maculopapular rashes and pruritus, which occur in a significant number of patients[86,87]. Endocrine disorders, especially those affecting the thyroid, adrenal, and pituitary glands, can lead to hypothyroidism and adrenal insufficiency, complicating treatment management [88,89].

Gastrointestinal reactions, including colitis and diarrhea, are also prevalent and can lead to significant morbidity if not managed promptly[87,89]. Given the wide range of possible irAEs, early recognition and intervention are critical to preventing long-term complications and ensuring the best possible outcomes for patients[86,88]. Corticosteroids are typically the first-line treatment for mild to moderate irAEs, while more severe reactions may require additional immunosuppressive therapies like tocilizumab or other agents[87,89]. The key to successful management lies in early identification of symptoms, patient education, and prompt intervention to prevent the progression of adverse events[87,89].

In the long term, some irAEs may persist and affect patients' quality of life. Chronic endocrine dysfunctions, for example, may require lifelong management, while psychological effects related to irAEs can further impact a patient's overall well-being[86,89]. Studies have indicated that while most irAEs are manageable, continuous monitoring and supportive care are essential for patients undergoing immunotherapy to ensure both their physical and mental health[87,89].

Prospective Insights into Tailoring Immunotherapy for RCC

Despite the remarkable progress in immunotherapy for RCC, challenges remain. A growing area of focus is tailoring treatments to individual patient profiles. Understanding the molecular and immunologic characteristics of the tumor, as well as patient-specific factors such as BMI, sarcopenia, and concomitant medications, will be key to optimizing treatment strategies. Biomarker-driven approaches are poised to play a crucial role in identifying the most effective therapies for each patient, minimizing unnecessary toxicities, and enhancing the overall treatment response. Additionally, the exploration of novel immune checkpoint inhibitors and combination regimens will continue to be a primary focus. By integrating new therapeutic targets like LAG-3 and TIGIT with existing therapies, future strategies may offer more robust and durable responses, particularly in patients who have shown resistance to current treatment options.

As the field continues to evolve, personalized treatment protocols based on comprehensive patient profiles and tumor characteristics will be essential to maximizing the therapeutic potential of immunotherapy in RCC.

Omics Approaches to Predicting and Enhancing ICI Efficacy in RCC

The integration of omics technologies in RCC research has opened new avenues for understanding the molecular mechanisms that govern tumor behavior and its response to ICI. These advanced techniques, including single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and whole exome sequencing (WES), have not only helped identify predictive biomarkers but also revealed complex resistance mechanisms. This section explores how these technologies contribute to personalized treatment strategies for RCC and how multi-omics approaches are shaping the future of ICI therapy in RCC. Recent Omics Studies of ICI in RCC are presented in **Table 2**

Table 2. Recent Omics Studies of ICI-Based Therapies in RCC.

Sample number	Control group	Experimental group	Experimental design	Refs	Data availability
8	ccRCC or type 2 papillary RCC, ICI-untreated	ccRCC or type 2 papillary RCC, ICI-treated	scRNAseq	166	dbGaP: phs002065.v1.p1
24	NA	ccRCC, ICI-treated	STseq	56	GSE175540
6	ccRCC, ICI-untreated	ccRCC, ICI-treated	scRNAseq	167	https://www.ncbi.nlm.nih.gov/sra/PRJNA705464
9	ANT and ccRCC, ICI-untreated	ccRCC, ICI-treated	scRNAseq	54	GSE210038
2	ccRCC, ICI-untreated	ccRCC, ICI-treated	STseq	168	GSE210041
2	ccRCC,Non-response to ICI treatment	ccRCC, response to ICI treatment	scRNAseq	169	EGAD00001008166
4	ccRCC, ICI-untreated	ccRCC, ICI-treated	scRNAseq	170	NA
4	NA	FHRCC, ICI-treated	scRNAseq	171	supplementary data
8	ccRCC or type 2 papillary RCC, ICI-untreated	ccRCC or type 2 papillary RCC, ICI-treated	WES	166	phs002065.v1.p1
220	NA	aRCC, ICI-treated	RNAseq	172	syn53162048
733	NA	aRCC, ICI-treated	WES	173	supplementary data
720	NA	aRCC, ICI-treated	RNAseq	173	supplementary data
46	mRCC, ICI-untreated	mRCC, ICI-treated	RNAseq	174	GSE67818
29	NA	ccRCC	RNAseq	167	https://www.ncbi.nlm.nih.gov/sra/PRJNA705464
60	ccRCC, ICI-untreated	ccRCC, ICI-treated	RNAseq	169	EGAD00001008163
13	NA	ccRCC	WES	169	EGAS00001005638

93	NA	ccRCC	TCRseq	[169]	EGAD00001008165
57	mRCC, ICI-untreated	mRCC, ICI-treated	RNAseq	[175]	E-MTAB-3218
70	normal tissue	metastatic ccRCC, ICI-treated	WES	[176]	NA
197	ccRCC and ccRCC, ICI-untreated	ccRCC, ICI-treated	RNAseq	[177]	phs003079.v1.p1
156	ccRCC and ccRCC, ICI-untreated	ccRCC, ICI-treated	WES	[177]	phs003079.v1.p1
28	mRCC, ICI-untreated	mRCC, ICI-treated	Circulating free DNA seq	[178]	NA
28	mRCC, ICI-untreated	mRCC, ICI-treated	WES	[178]	NA
72	Renca tumours from mice, ICI-untreated	Renca tumours from mice, ICI-treated	RNAseq	[179]	GSE153941

Abbreviation: ccRCC: clear cell renal cell carcinoma, ANT: adjacent non-tumor tissue, FHRCC: fumarate hydratase-deficient renal cell carcinoma, aRCC: advanced renal cell carcinoma, mRCC: metastatic renal cell carcinoma, ICI: immune checkpoint inhibitor, scRNAseq: single-cell RNA sequencing, STseq: spatial transcriptome sequencing, WES: whole exome sequencing, TCRseq: T cell receptor sequencing, RNAseq: RNA sequencing.

Predictive Biomarkers of ICI Response in RCC

The identification of reliable predictive biomarkers is critical for optimizing ICI therapy in RCC. PD-L1 expression remains a cornerstone biomarker, as tumors with high PD-L1 expression often show better responses to PD-1/PD-L1 inhibitors by promoting immune evasion through inhibition of T-cell activation. However, the predictive value of PD-L1 is context-dependent, varying with tumor subtype and individual patient factors[90].

Tumor mutational burden (TMB) is another promising biomarker. Higher TMB indicates a greater number of mutations in the tumor's genome, which increases the likelihood of neoantigen formation—targets for the immune system. In RCC, elevated TMB correlates with improved response rates to ICI, as more neoantigens make the tumor more immunogenic[91]. Similarly, microsatellite instability (MSI), especially in MSI-high tumors, has been shown to predict favorable responses to ICI. MSI-high tumors are generally more immunogenic and respond better to therapies targeting the PD-1/PD-L1 axis[92].

However, no single biomarker can predict ICI efficacy with absolute certainty. A composite biomarker approach, integrating multiple biomarkers such as PD-L1, TMB, and MSI, along with immune signatures, may offer a more accurate prediction of ICI response and help guide treatment decisions in RCC.

Omics Advances: Dissecting Tumor Immunity and Resistance

Despite the success of ICI in many RCC patients, a substantial proportion show primary resistance or acquired resistance over time. Understanding the mechanisms behind this resistance is key to improving treatment outcomes. Recent single-cell RNA sequencing (scRNA-seq) studies have revealed how ICI reshape the RCC tumor microenvironment

(TME). ICI impact the interactions between tumor cells and immune cells, influencing both the immune response and the resistance mechanisms. Specifically, tissue-resident T cells and tumor-associated macrophages (TAMs) play crucial roles in modulating the effectiveness of ICI [93] [94].

Furthermore, the functional status of tumor-infiltrating lymphocytes (TILs), including CD4+ and γ/δ T cells, has been associated with ICI responsiveness [94,95]. Recent studies also suggest that maintaining or enhancing pre-existing immune responses could be pivotal for the success of anti-PD-1 therapy, as indicated by T-cell receptor (TCR) sequencing [96].

However, the presence of intratumoral heterogeneity (ITH) is a significant challenge. High levels of ITH have been associated with immune evasion, making tumors more resistant to ICI treatment[97]. Identifying markers of ITH could provide a deeper understanding of treatment resistance and guide the development of strategies to overcome it.

Spatial transcriptomics has further expanded our understanding by revealing the role of tertiary lymphoid structures (TLS) in B-cell maturation and antibody production, both of which are crucial for effective antitumor immunity[56]. Interestingly, the spatial organization of mesenchymal-like ccRCC cells and myCAF (myofibroblastic cancer-associated fibroblasts) has been implicated in ICI resistance, suggesting that the TME's structural and cellular composition plays a key role in modulating therapeutic outcomes[54].

Molecular Profiling and Precision Medicine in RCC

In addition to identifying biomarkers of response and resistance, omics technologies such as whole exome sequencing (WES) and bulk RNA sequencing have provided detailed insights into the molecular profiles of RCC tumors. WES has identified mutations in genes such as PTEN, ABCA1, and DNMT1, which could influence treatment response and help tailor personalized therapies for RCC patients[98]. For instance, loss of the gene PBRM1 in clear cell RCC (ccRCC) has been shown to alter the expression profile of tumor cells, potentially affecting the tumor's response to ICI[99].

While tissue-based WES offers valuable insights into the mutational landscape of RCC, it may not capture the dynamic changes occurring within the tumor or the heterogeneity of the immune response. In this regard, circulating tumor DNA (ctDNA) analysis offers a promising non-invasive alternative. Studies have shown that ctDNA dynamics can be used as a real-time predictive marker for ICI efficacy, enabling early detection of treatment resistance[100].

In addition, bulk RNA sequencing has identified key genetic signatures related to immune pathways and angiogenesis, offering novel insights into the molecular mechanisms that govern ICI efficacy. Integrating these genetic signatures with spatial maps of the immune microenvironment can help define personalized treatment strategies and optimize patient selection for ICI [98,101].

Furthermore, profiling the molecular response and resistance mechanisms to nivolumab in metastatic ccRCC has provided crucial insights into patient selection for first-line treatments[102]. Likewise, studies of sunitinib treatment have demonstrated how TKIs can impact the expression of key genes involved in immune modulation and tumor progression, influencing both treatment efficacy and resistance [103].

Prospective Insights into Multi-Omics Approaches and Personalized ICI Therapy

As we move toward more personalized treatment strategies in RCC, multi-omics approaches are essential for identifying the most promising biomarkers and understanding the complexities of treatment resistance. Future research will focus on refining liquid biopsy techniques, such as ctDNA analysis, to provide real-time insights into treatment efficacy[104]. Moreover, nanostring sequencing and other high-throughput technologies are poised to uncover novel transcriptomic signatures of immune escape, which could be used to predict ICI response[97].

Ultimately, a deeper understanding of the tumor microenvironment, immune evasion mechanisms, and molecular profiles will enable the development of more effective, tailored therapies. By integrating omics data with clinical characteristics, we can enhance the precision and efficacy of ICI treatments, improving outcomes for RCC patients and advancing the field of precision oncology.

The Application of Artificial Intelligence (AI) in Immune Checkpoint Inhibitor (ICI) Therapy for Renal Cell Carcinoma (RCC)

Current Applications: AI Leading the New Era of Personalized Immunotherapy

The integration of artificial intelligence (AI) into personalized immunotherapy, particularly in the realm of immune checkpoint inhibitors (ICIs), is poised to transform the treatment landscape for renal cell carcinoma (RCC). This approach encompasses various methodologies, including the development of tailored immunotherapeutic strategies, predicting patient responses to ICIs or CAR-T cell therapies, and leveraging AI to screen novel immunotherapeutic agents. AI's capacity to analyze vast datasets and identify hidden patterns has the potential to significantly enhance our understanding of tumor biology and the immune microenvironment, ultimately leading to more effective and personalized treatment protocols for RCC patients[105–107].

Recent advancements have demonstrated the utility of AI in predicting immunotherapy responses. For instance, AI algorithms can analyze genomic and transcriptomic data to identify biomarkers that correlate with patient outcomes. This capability is particularly crucial, as a significant proportion of RCC patients fail to respond to current immunotherapeutic options, highlighting the need for more precise patient stratification[105,106]. Furthermore, AI in immunogenomics enables the identification of tumor-specific neoantigens, which can be targeted in personalized treatment regimens[108].

Additionally, the combination of AI with traditional immunotherapy approaches, such as ICIs, is being explored to improve therapeutic efficacy. Studies have shown that combining ICIs with other modalities, including anti-angiogenic therapies, can lead to improved outcomes in advanced RCC[109,110]. AI-driven insights into the synergistic effects of such combinations may pave the way for more robust treatment strategies that address the complexities of RCC.

Beyond response prediction, AI can also aid in identifying novel therapeutic targets. By analyzing the tumor immune microenvironment, AI can reveal mechanisms of immune evasion employed by RCC cells, which is crucial for the development of effective combination therapies[111,112]. Understanding these mechanisms is essential for designing treatment protocols that not only directly target the tumor but also enhance the immune system's ability to recognize and eliminate cancer cells.

As the field of immunotherapy continues to evolve, the integration of AI technologies will be instrumental in overcoming the challenges associated with RCC treatment. AI's potential to refine patient selection, optimize treatment combinations, and predict therapeutic responses marks a significant step forward in the pursuit of personalized cancer care. Future research will undoubtedly focus on harnessing these technologies to improve clinical outcomes for RCC patients, thereby transforming the therapeutic landscape for this challenging malignancy[113,114].

Predicting ICI and CAR-T Efficacy: AI's Cutting-Edge Predictive Capabilities

The prediction of patient responses to immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapies has emerged as a pivotal area of research in oncology. Recent advancements in artificial intelligence (AI), particularly through machine learning and deep learning techniques, have shown promise in analyzing clinical data and biological markers to improve the accuracy of these predictions. By leveraging large datasets, these AI-driven approaches can identify patterns and correlations that may not be immediately evident through traditional analytical methods, thus assisting clinicians in selecting the most appropriate treatment strategies for individual patients[115–117].

For instance, a deep learning model was employed to predict treatment outcomes for patients with non-small cell lung cancer (NSCLC) undergoing PD-1 blockade. This model utilized radiology reports to forecast best overall responses and progression-free survival, showcasing AI's potential in real-world clinical settings[118]. Similarly, another study integrated clinical and genomic data to construct a predictive model for ICI efficacy in NSCLC, revealing that tumor mutational burden and PD-L1 expression are key factors

influencing treatment outcomes[119,120].

Moreover, machine learning classifiers have proven valuable in identifying patients likely to benefit from immunotherapy. For example, a study utilized a 24-gene RNA signature to predict durable clinical benefits in patients with gastrointestinal cancers treated with ICIs, demonstrating the potential of genomic profiling in enhancing predictive accuracy[121]. Incorporating tumor microenvironment characteristics into predictive models has also been shown to improve the identification of patients who may respond favorably to ICIs[117,122].

AI also plays a crucial role in refining the prediction of treatment responses by integrating longitudinal data, including changes in radiomic features and immune cell profiles. A study demonstrated that changes in CT radiomic features, such as lymphocyte distribution, could predict overall survival and immunotherapy response in NSCLC patients, emphasizing the importance of dynamic assessments in treatment planning[123,124].

In conclusion, the application of AI and machine learning techniques to predict responses to ICIs and CAR-T therapies holds substantial promise. By leveraging clinical data, genomic information, and advanced computational models, clinicians can make more informed decisions, ultimately leading to improved patient outcomes and personalized treatment approaches [115,116,125].

Accelerating the Development of New Immunotherapeutic Agents: AI in Drug Discovery

To expedite the development of new immunotherapeutic agents, several methodologies can be employed to identify promising drug candidates. One promising approach involves the integration of artificial intelligence (AI) with high-throughput screening techniques. By analyzing vast datasets of chemical and biological information, AI can effectively identify compounds that may possess immunomodulatory properties. This computational strategy not only streamlines the drug discovery process but also enhances the likelihood of discovering novel immunotherapeutics that can be validated through experimental methods[126–128].

High-throughput screening platforms, such as the High-Throughput Immunomodulator Phenotypic Screening Platform (HTiP), have been developed to model the complex interactions within the cancer-immune microenvironment. These platforms allow for the simultaneous testing of numerous compounds, facilitating the identification of small-molecule immunomodulators that can enhance anti-tumor immune responses. For example, the HTiP platform has successfully identified inhibitors of apoptosis proteins (IAPs) as potential anti-cancer immune enhancers, highlighting the effectiveness of this approach in discovering new therapeutic agents[129–131].

Moreover, co-culture systems that mimic the tumor microenvironment have significantly improved the identification of immunotherapeutic candidates. By co-culturing cancer cells with immune cells, researchers can observe how various compounds interact with and modulate immune responses. This method has proven valuable in identifying drugs that can reprogram immune responses to better target tumors, enhancing the efficacy of existing therapies[132,133].

In addition to these experimental approaches, drug repurposing offers a time-efficient strategy for discovering new immunotherapeutics. By screening libraries of FDA-approved drugs, researchers can identify compounds that may have previously unrecognized immunomodulatory effects. For example, a study found that Adefovir Dipivoxil, an approved drug, significantly inhibited T-cell proliferation, suggesting its potential application in treating T-cell-mediated autoimmune diseases [134]. This strategy not only reduces the time and cost associated with drug development but also leverages existing safety data for rapid clinical application.

Furthermore, the application of machine learning algorithms to predict drug-target interactions has enhanced the identification of suitable candidates for immunotherapy. By utilizing publicly available bioactivity data, researchers can generate hypotheses regarding potential therapeutic targets, thereby prioritizing compounds for further investigation[135,136].

In summary, the combination of AI-driven analysis, high-throughput screening, co-culture systems, drug

repurposing, and machine learning represents a multifaceted strategy to expedite the identification of novel immunotherapeutic agents. These methodologies not only enhance the efficiency of the drug discovery process but also hold the promise of uncovering new treatments that can improve patient outcomes in cancer therapy and other immune-related diseases.

Personalizing ICI Therapy: AI in Precision Targeted Immunotherapy

Personalized immunotherapy strategies are increasingly being designed based on individual biomarkers and genomic information. This approach aims to maximize therapeutic efficacy while minimizing adverse effects. The integration of artificial intelligence (AI) into this process can significantly enhance the analysis of vast genomic datasets, facilitating the identification of potential immune checkpoint targets. For example, AI algorithms can analyze a patient's genomic data to predict which immune checkpoint inhibitors are most likely to be effective, thereby enabling a more precise treatment strategy[137–140].

Recent advances in immunogenomics emphasize the importance of understanding the tumor's genetic landscape and its interactions with the immune system. The identification of neoantigens—mutated peptides recognized as foreign by the immune system—has become a focal point in developing personalized vaccines and therapies. These neoantigens, derived from a patient's unique tumor mutations, can be identified more efficiently through AI-driven genomic analysis[141–143]. Leveraging next-generation sequencing technologies, researchers can map these mutations and design targeted therapies that harness the patient's immune response against their specific tumor profile[144–146].

Furthermore, exploring combination therapies that integrate ICIs with other treatment modalities, such as chemotherapy or targeted therapies, is gaining traction. This strategy aims to overcome resistance mechanisms that tumors may develop against single-agent therapies. AI plays a pivotal role in predicting which combinations may yield the best outcomes based on the genomic and immune profiles of patients[147,148]. The ability to analyze complex datasets and identify patterns that correlate with treatment responses is crucial for advancing personalized cancer care.

In addition, novel AI tools will provide guidance for precision treatment. For instance, TCellSI, a novel computational tool leveraging Mann-Whitney U statistics, quantifies eight distinct T cell states—Quiescence, Regulating, Proliferation, Helper, Cytotoxicity, Progenitor exhaustion, Terminal exhaustion, and Senescence—from transcriptomic data[149]. In renal cell carcinoma (RCC), TCellSI demonstrates significant potential in predicting responses to immune checkpoint blockade (ICB) therapy. By assessing effector T cell states (e.g., Cytotoxicity, Proliferation, and Terminal exhaustion), TCellSI identifies patients with enhanced immune activation and improved overall survival following ICB treatment. Furthermore, its scores correlate strongly with immune infiltration and antitumor pathway activity, reflecting the tumor immune microenvironment. These features position TCellSI as a robust biomarker for stratifying RCC patients likely to benefit from ICB therapy, offering valuable insights for personalized immunotherapy strategies.

In conclusion, the future of cancer treatment lies in the ability to personalize immunotherapy based on individual genomic and immune characteristics. AI technologies are poised to revolutionize this field by providing insights that guide the selection of the most effective therapies, ultimately improving clinical outcomes and deepening our understanding of tumor-immune interactions[150–152].

Current Challenges and Future Directions in Immunotherapy for RCC

The Challenge of Resistance Mechanisms

Immune checkpoint inhibitors (ICI) have revolutionized the treatment of advanced renal cell carcinoma (RCC), but the emergence of both primary and acquired resistance to ICI represents a significant clinical hurdle. While ICI have shown promising results in many patients, their efficacy can be limited due to the heterogeneity of RCC and complex interactions within the tumor microenvironment (TME). Research has elucidated several key resistance mechanisms:

Insufficient antigen recognition by T cells and impaired T-cell infiltration into the tumor are primary factors contributing to

resistance[153]. In some cases, T-cell dysfunction within the TME reduces their cytotoxicity, undermining the immune response to tumor cells.

The TME itself plays a critical role in promoting resistance, as it can foster an immunosuppressive environment that inhibits the action of ICI[154]. This includes the presence of regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), all of which contribute to immune evasion mechanisms within the tumor.

Understanding these mechanisms in greater depth is critical for designing strategies to overcome resistance. It is becoming increasingly clear that combination therapies—which target multiple aspects of tumor biology and immune escape mechanisms—may offer the best strategy for improving the efficacy of ICI in RCC. For instance, combining ICI with agents that modify the TME, such as anti-angiogenics, or those that enhance T-cell activity, could potentially overcome these resistance barriers[155]. As research continues, identifying predictive biomarkers for these resistance mechanisms will be crucial for selecting patients who are more likely to benefit from such combination therapies.

Promising Novel Combination Therapies

In recent years, the exploration of novel combination therapies has gained significant attention as a promising approach to enhance the therapeutic potential of ICI in advanced RCC[156]. Several combination strategies are currently under investigation: (1) ICI and Anti-Angiogenic Combinations: Combining ICI with anti-angiogenic therapies, such as TKIs or monoclonal antibodies targeting VEGF, has shown synergistic effects[157]. This combination not only targets the tumor directly but also modulates the TME, making it more favorable for immune cell infiltration and activity. (2) Immunotherapy and Oncolytic Viruses: Another novel approach includes the use of oncolytic viruses that selectively infect and destroy tumor cells while simultaneously activating an immune response against the tumor[158]. Early-phase studies indicate that combining oncolytic viruses with ICI can amplify the anti-tumor immune response. (3) T-cell-based therapies and Bispecific Antibodies: Combining ICI with CAR-T cell therapy or bispecific antibodies targeting both tumor antigens and immune cells offers the potential for more robust immune activation[159]. These strategies aim to direct the immune response more specifically toward tumor cells, potentially overcoming resistance and improving therapeutic outcomes.

Ongoing clinical trials exploring these combination regimens will provide critical insights into their clinical utility and may lead to the identification of more effective, personalized treatment protocols for RCC. These advancements could reshape the treatment landscape for advanced RCC and increase the likelihood of durable responses in patients.

Economic and Ethical Challenges

Despite the promising advancements brought by ICI, their widespread adoption is constrained by significant economic challenges. The high cost of ICI presents a substantial barrier to access, especially in low- and middle-income countries[160]. Additionally, these therapies often yield variable outcomes, which raises concerns about their cost-effectiveness.

As ICI become more integrated into standard practice, there is an urgent need for comprehensive cost-effectiveness analyses to guide healthcare policy and ensure that resources are allocated efficiently[161]. Furthermore, ethical considerations must be addressed to ensure equitable access to these life-saving therapies. This includes the development of fair pricing models, reimbursement strategies, and support programs that help economically disadvantaged patients access ICI[162]. The implementation of these solutions will be essential in promoting global health equity and ensuring that the benefits of immunotherapy are accessible to all patients, regardless of their economic status.

Prospective Insights into Precision Medicine and Multi-Omics Approaches

Looking ahead, the future of ICI therapy in RCC lies in the integration of precision medicine and multi-omics approaches. With the advent of technologies such as single-cell RNA sequencing, spatial transcriptomics, and liquid biopsy, there is a growing opportunity to tailor therapies more precisely based on an individual patient's tumor profile and immune microenvironment. Key future directions include: (1)

Identification of Predictive Biomarkers: Reliable biomarkers are crucial to predict which patients will benefit from ICI. Beyond traditional biomarkers like PD-L1 expression and TMB, emerging markers based on tumor-infiltrating lymphocytes (TILs), T-cell receptor (TCR) sequencing, and spatial patterns of immune cell distribution are showing promise in guiding treatment decisions. (2) Understanding Tumor Heterogeneity: One of the challenges in RCC is the intratumoral heterogeneity (ITH) that contributes to resistance. Next-generation sequencing technologies, such as whole exome sequencing (WES) and circulating tumor DNA (ctDNA) analysis, offer real-time insights into tumor evolution, enabling clinicians to monitor disease progression and identify dynamic changes in the tumor genome. (3) Combining Immunotherapy with Other Modalities: Future therapies will likely involve combinations of ICI with targeted therapies, radiotherapy, or novel immune-modulatory agents to enhance efficacy and minimize resistance. Integrating these modalities in a rational manner, based on each patient's molecular and immune profile, holds great promise for improving long-term outcomes.

Conclusions and Perspectives

In summary, while immune checkpoint inhibitors have revolutionized the treatment of advanced RCC, overcoming resistance remains one of the greatest challenges in maximizing their clinical efficacy. Future research should prioritize the identification of novel resistance mechanisms and the development of effective combination therapies to circumvent these hurdles. Moreover, multi-omics approaches and precision medicine will be pivotal in tailoring treatments to individual patient characteristics, optimizing efficacy, and minimizing side effects. With ongoing advancements in technology and a deeper understanding of tumor immunology, the future of ICI therapy in RCC looks promising, with the potential for even more refined and personalized treatment strategies that can ultimately improve patient survival and quality of life.

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COMPETING INTERESTS

All authors declare that they have no conflict of interest.

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