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Review

Immunotherapy in Renal Cell Carcinoma: Modulating the Tumor Microenvironment, Overcoming Resistance Mechanisms, and Implementing Biomarker-Guided Combination Treatments

Running Title: Immunotherapy in Renal Cell Carcinoma

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Abstract: Renal cell carcinoma (RCC) is distinguished by a highly inflamed tumor microenvironment (TME) that offers both opportunities and challenges for immunotherapy. This review synthesizes current insights into the immunological landscape of RCC, highlighting robust cluster of differentiation 8-positiv ($CD8^+$) T-cell infiltration, unconventional antigen sources such as endogenous retroviruses and frameshift neoantigens, and the heterogeneity of immune niches revealed by single-cell and spatial profiling. We then examine the clinical impact and mechanisms of immune checkpoint inhibitors —including programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)— tumor vaccines, cellular therapies such as chimeric antigen receptor T cell (CAR-T) therapy and tumor-infiltrating lymphocytes (TILs) and bispecific antibody constructs, emphasizing advances in dosing, engineering, and combination regimens. Combination strategies—including dual checkpoint blockade, integration with anti-angiogenic tyrosine kinase inhibitors, radiotherapy, metabolism-targeted agents such as adenosine and poly (ADP-ribose) polymerase (PARP) inhibitors, and hypoxia modulators—are reviewed for their capacity to overcome resistance and remodel the microenvironment. We further explore intrinsic and acquired resistance mechanisms, the immunosuppressive roles of myeloid and stromal elements, and emerging biomarker approaches spanning genomic, transcriptomic, spatial, and circulating analytes. Finally, we discuss current limitations—such as variable clinical response, toxicities, and biomarker gaps—and outline future prospects, including personalized combination regimens, next-generation engineered cell products, and artificial intelligence (AI)-driven precision monitoring. Together, these insights chart a path toward more effective, individualized immunotherapy in RCC.

Keywords: renal cell carcinoma; immunotherapy; tumor microenvironment; immune checkpoint inhibitors; combination therapy; resistance mechanisms; biomarkers; CAR-T cell therapy; tumor vaccines; bispecific antibodies

1. Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney and remains a significant cause of cancer-related morbidity and mortality worldwide [1–5]. Among its histologic subtypes, clear-cell RCC (ccRCC) is notable for its frequent dysregulation of hypoxia pathways—most often due to von Hippel–Lindau (VHL) loss—and for harboring one of the highest degrees of immune infiltration among solid tumors [1,6–9]. Paradoxically, despite abundant tumor-infiltrating lymphocytes (TILs), ccRCC often establishes a profoundly immunosuppressive microenvironment through upregulation of inhibitory checkpoints (e.g., programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen-4 (CTLA-4)) and secretion of suppressive cytokines, enabling tumor immune escape and limiting the efficacy of host antitumor immunity.

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the therapeutic landscape of metastatic RCC, delivering durable responses in a subset of patients that were previously refractory to conventional therapies [10]. In the Phase III JAVELIN Renal 101 trial, avelumab + axitinib (targeting PD-L1 and Vascular Endothelial Growth Factor Receptor [VEGFR]) significantly improved progression-free survival (PFS) and objective response rate (ORR) compared with sunitinib in PD-L1$^+$ patients—median PFS 13.8 vs. 7.2 months (HR 0.61); overall survival (OS) did not reach statistical significance at final analysis [10]. Similarly, CheckMate 214 demonstrated that nivolumab + ipilimumab (targeting PD-1 and CTLA-4) yielded superior OS (HR 0.69), higher ORR (42.4% vs. 27.5%), and durable responses versus sunitinib in intermediate-/poor-risk RCC, with 8-year follow-up confirming sustained benefit [11,12]. These dual-checkpoint strategies have become foundational in RCC and have catalyzed broader immunotherapeutic advances, including tumor vaccines, cellular therapies (CAR-T, TILs), and bispecific antibodies designed for enhanced specificity and combinatorial synergy [13–16]. Agents targeting the PD-1/PD-L1 and CTLA-4 axes have improved overall survival compared with prior standards of care, leading to multiple U.S. Food and Drug Administration (FDA)-approved combinations in the first-line setting [1].

Despite these advances, 30–40% of patients derive only limited benefit, and both innate and acquired resistance remain major obstacles [17,18]. Mechanisms of resistance include antigen-presentation defects (β2-microglobulin loss), activation of alternative checkpoints (lymphocyte-activation gene 3 [LAG-3], T cell immunoreceptor with Ig and ITIM domains [TIGIT]), hypoxia-driven metabolic suppression, and exclusionary stromal barriers [19–23].

In this review, we comprehensively examine the immunobiology of RCC—detailing the composition and functional states of key immune cell populations, checkpoint landscapes, and tumor-intrinsic antigen sources. We then outline both established and emerging immunotherapies—from ICIs to personalized vaccines, adoptive cellular therapies, and bispecific constructs—and discuss the rationale for combining these with anti-angiogenic agents, radiotherapy, and metabolic modulators. In particular, we highlight the promise of post-surgical vaccine strategies for preventing recurrence and chart future directions for their clinical integration. Finally, we explore mechanisms of resistance and biomarker challenges, and propose integrated, personalized combination approaches.

2. Characteristics of Renal Cell Carcinoma and Challenges in Immunotherapy

2.1 Immunological Features of Renal Cell Carcinoma (Highly Immune-Infiltrated "Hot" Tumor)

Clear-cell RCC is among the most immunologically infiltrated solid tumors, comprising high densities not only of CD8$^+$ tumor-infiltrating lymphocytes (TILs) but also of CD4$^+$ T cells, NK cells, tumor-associated macrophages (TAMs), dendritic cells, and other immune subsets, each exerting distinct influences on prognosis and therapeutic sensitivity [24–28]. Beyond overall T-cell abundance, a claudin-low molecular subset of ccRCC exhibits both poor survival and distinct tumor microenvironment characteristics—underscoring the heterogeneity within this “hot” phenotype [11,25]. Paradoxically, many CD8$^+$ TILs co-express exhaustion markers (PD-1, CTLA-4), and multiplex immunohistochemistry together with spatial transcriptomics has revealed discrete “immunosuppressive niches” where CD39$^+$PD-1$^+$ T cells co-localize with FoxP3$^+$ regulatory T cells, correlating with poorer survival [27–29]. Hypoxia-inducible factor (HIF)–driven expression of endogenous retroviruses (e.g., ERVE-4) and frameshift-derived neoantigens further diversify the antigenic milieu and are linked to enhanced ICI responsiveness in high-ERV tumors [30–34].

Having established ccRCC’s heterogeneous “hot” immune environment, we next examine how these cell populations and antigenic features translate into clinical responses to checkpoint and combination regimens.

High-resolution single-cell and spatial analyses have revealed extensive intratumoral heterogeneity in both immune and tumor compartments. Paired single-cell RNA and T-cell

receptor sequencing of multiple tumor regions, draining lymph nodes, normal kidney, and blood from ccRCC patients revealed enrichment of tissue-resident $CD8A^+$cells in checkpoint-blockade responders, whereas non-responders showed macrophage-dominated landscapes [26]. Multiplex immunohistochemistry further distinguished tumor-reactive ($CD39^+PD\text{-}1^+$) from bystander $CD8^+$ T cells, mapping them alongside $FoxP3^+$ regulatory T cells into discrete immunosuppressive "hotspots" whose abundance correlates with poorer survival [27–29].

Tumor-intrinsic antigen sources in ccRCC extend beyond classic neoantigens. Hypoxia-inducible factor (HIF) drives expression of endogenous retroviruses (ERVs) such as ERVE-4, which generate HLA-presented peptides recognized by T cells [30] . High ERV expression predicts better ICI responses, and a dual-ERV stratification system predicts immunotherapy efficacy in metastatic ccRCC [31,32]. Frameshift-derived neoepitopes from small INDELs likewise elicit robust T-cell responses despite moderate tumor mutational burden [33,34].

Molecular subtyping further refines the ccRCC immune landscape. The Immunity-High/L classification defines tumors with high immune infiltration yet pronounced $CD8^+$ T-cell exhaustion and M2-like TAM enrichment; these tumors exhibit reduced responsiveness to nivolumab + ipilimumab and minimal benefit from sunitinib monotherapy [35,36]. Conversely, Immunity-Low tumors display angiogenesis-driven biology, derive greater benefit from combined ICI + VEGF-TKI regimens, and demonstrate sensitivity to sunitinib monotherapy [35,36]. The metabolic–immune M1–M4 framework identifies an "immune-inflamed, metabolic-desert" M3 subset with the most favorable ICI responses, whereas the VHL-mutant–enriched M2 subset—characterized by high metabolic activity and low immune infiltration—shows superior responsiveness to sunitinib but reduced ICI efficacy [37].

Single-cell RNA-seq and spatial transcriptomics have refined the delineation of T-cell states in ccRCC. Exhausted T cells, characterized by high PD-1, LAG-3, and T cell immunoglobulin and mucin-domain containing-3 [TIM-3] expression, predominate in densely tumorous, immunosuppressive niches and exhibit reduced effector function [38]. In contrast, stem-like T cells expressing TCF-1 localize to supportive niches, retain proliferative potential, and can replenish effector pools—features linked to sustained antitumor activity [39]. Multiregional scRNA mapping further connects these stem-like populations to distinct tumor topologies and therapy outcomes [14], while spatial analyses reveal discrete intra-tumoral zones favoring either exhaustion or stem-like profiles [40].

Figure 1 clearly demonstrates ccRCC as the most heavily infiltrated ("hottest") tumor, descending through melanoma, NSCLC, breast, to colorectal.

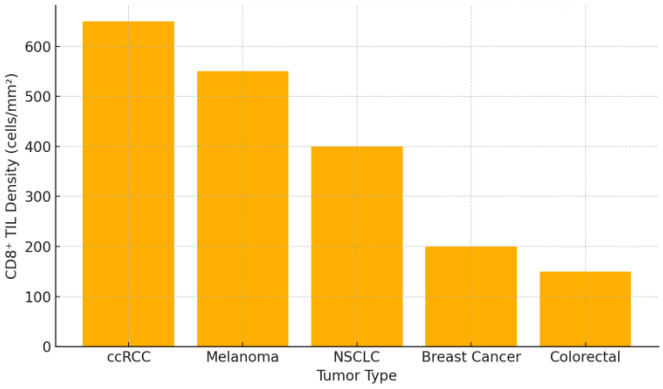

Figure 1. CD8+ TIL Infiltration Across Tumor Types

2.2 Immunotherapy Response and Immunogenomic Subtypes

First-line combinations of immune checkpoint inhibitors (ICIs) with VEGF-tyrosine kinase inhibitors (TKIs) have markedly improved outcomes in advanced ccRCC. In the phase 3 CheckMate 9ER trial, nivolumab plus cabozantinib achieved a median progression-free survival (PFS) of 16.6 months, an objective response rate (ORR) of 55.7–56% and a complete response (CR) rate of 13%, with a median duration of response (DOR) of 22.1 months across International Metastatic RCC Database Consortium (IMDC) risk groups and PD-L1 status [19,41–43]. In JAVELIN Renal 101, avelumab plus axitinib extended PFS to 13.8 months and yielded an ORR of 59.7% overall (55.2% in PD-L1 + patients), with a five-year PFS rate of 12% versus 4.4% for sunitinib [10,39]. The KEYNOTE-426 study demonstrated that pembrolizumab plus axitinib conferred a PFS of 15.4 months, an ORR of 60%, a CR rate of 9%, and a median DOR of 24 months [44,45].

Molecular subtyping further refines the ccRCC immune landscape and predicts differential therapeutic benefit. The Immunity-High/L subtype (Braun DA et al., Cancer Cell 2021) is characterized by high immune infiltration accompanied by terminally exhausted $CD8^+$ T cells and M2-like macrophage predominance; these tumors exhibit reduced responsiveness to dual ICI (nivolumab + ipilimumab) and derive minimal benefit from sunitinib monotherapy [35,36]. In contrast, Immunity-Low tumors display angiogenesis-driven biology and greater sensitivity to combined ICI + VEGF-TKI regimens [35,36]. The metabolic–immune M1–M4 framework (Wang et al., Front Immunol 2022) identifies an "immune-inflamed, metabolic-desert" M3 subset with the most favorable responses to ICI, whereas the VHL-mutant–enriched M2 subset—marked by

high metabolic activity and low immune infiltration—shows superior responsiveness to sunitinib but reduced ICI efficacy [37].

These immunogenomic classifications align with clinical trial outcomes and support a precision-medicine approach, whereby patients with Immunity-High/L or M3 tumors are prioritized for ICI-based regimens, while those with Immunity-Low or M2 tumors may benefit more from early incorporation of VEGF-TKIs or TKI monotherapy.

Table 1 provides a comparative overview of current RCC immunotherapies—approved agents and late-stage clinical combinations—detailing target cell types, mechanisms of action, clinical efficacy outcomes, and reported immune-related adverse events (AEs).

Table 1. Comparative Summary of RCC Immunotherapies.

	Therapy	Target Molecule(s)	Mechanism of Action	PFS (months)	ORR (%)	CR (%)	Immune-Related AEs
1	Nivolumab monotherapy	PD-1	PD-1 blockade; reverses T-cell exhaustion	4.6	25	1	Low–Moderate
2	Nivolumab + Cabozantinib	PD-1, VEGFR	PD-1 blockade + VEGF inhibition	16.6	56	13	Moderate–High
3	Avelumab + Axitinib	PD-L1, VEGFR	PD-L1 blockade + VEGF inhibition	13.8	59.7	Not specified	Moderate–High
4	Pembrolizumab + Axitinib	PD-1, VEGFR	PD-1 blockade + VEGF inhibition	15.4	60	9	Moderate–High
5	Nivolumab + Ipilimumab	PD-1, CTLA-4	Dual PD-1 and CTLA-4 blockade	Not specified	42.4	11.8	High

3. Main Immunotherapy Strategies

3.1 Immune Checkpoint Inhibitors

3.1.1 Mechanism of Action and Clinical Trials of PD-1/PD-L1 Inhibitors (e.g., Nivolumab, Pembrolizumab)

PD-1/PD-L1 inhibitors unleash antitumor T-cell activity by blocking the engagement of PD-1 on T cells with PD-L1 on tumor and stromal cells, thereby reversing T-cell exhaustion and restoring cytotoxic function [46]. Nivolumab demonstrated a median overall survival benefit versus everolimus in the phase III CheckMate 025 trial for advanced RCC, establishing PD-1 blockade as a new standard of care [46]. Pembrolizumab likewise has shown efficacy across malignancies in the KEYNOTE series, and is approved as first-line therapy for RCC in combination regimens [47].

Several recent phase II/III studies have refined dosing and sequencing to maximize efficacy while mitigating immune-related adverse events (irAEs). The TITAN-RCC trial employed nivolumab monotherapy with ipilimumab "boosts" in non-responders, improving objective response rates without unacceptable toxicity [48]. The PRISM trial's modified ipilimumab schedule (once every 12 weeks versus every 3 weeks) combined with nivolumab reduced grade 3–5 treatment-related adverse events without compromising response or survival [49]. The REFINE basket trial randomized responders to maintenance nivolumab at 4- versus 8-week intervals, demonstrating maintained efficacy and suggesting potential for reduced irAE burden and improved quality of life [50].

Translational efforts have further optimized PD-L1 antibodies via Fc and glycoengineering. An afucosylated avelumab variant exhibited enhanced FcγRIIIa binding, boosted antibody-dependent cellular cytotoxicity, and increased T-cell infiltration in preclinical models [51] De-fucosylated anti–PD-L1 antibodies also demonstrated superior $CD8^+$ T-cell activation and antitumor activity versus glycosylated counterparts, underscoring the role of antibody glycosylation in therapeutic potency [52].

Real-world analyses confirm trial findings in broader RCC populations. ASCO guidelines note that PD-1/PD-L1 inhibitors retain survival benefits and manageable irAE profiles outside clinical trials [19]. UK cohort data showed nivolumab monotherapy's safety mirrored CheckMate 025, while real-world combinations with tyrosine kinase inhibitors exhibited increased grade 3–4 toxicities consistent with pivotal studies [41,53–55]. A recent network meta-analysis reinforced that PD-1/PD-L1 regimens achieve durable responses with acceptable safety across diverse patient subgroups [56].

Additional co-inhibitory ligands modulate PD-1/PD-L1 efficacy. PD-L2 expression contributes to immune evasion and may necessitate dual PD-1/PD-L2 targeting to overcome resistance [57]. B7 homolog 3 (B7-H3; CD276) overexpression correlates with aggressive RCC phenotypes and reduced nivolumab responsiveness; targeting B7-H3 is under clinical investigation to enhance outcomes [58–60].

3.1.2 CTLA-4 Inhibitors and Combination Therapies

CTLA-4 blockade with ipilimumab augments T-cell priming by preventing CTLA-4–mediated attenuation of CD28 costimulation, thereby broadening the antitumor T-cell repertoire [61].

In advanced RCC, the combination of nivolumab and ipilimumab in the CheckMate 214 trial established a first-line standard for intermediate- and poor-risk patients: it achieved an objective response rate of 42.4% versus 27.5%, a complete response rate of 11.8% versus 2.6%, and a median duration of response of 82.8 versus 19.8 months in the IMDC intermediate/poor-risk subgroup; median overall survival was 46.7 months with nivolumab + ipilimumab versus 26.0 months with sunitinib (HR 0.69; 95% CI 0.59–0.81) at eight-year follow-up [38,62,63].

The American Society of Clinical Oncology guideline recommends this regimen for intermediate- and poor-risk metastatic clear-cell RCC, highlighting its durable benefit and manageable safety profile [64]. To mitigate toxicity, the PRISM trial evaluated an extended-interval ipilimumab schedule (12-weekly vs. 3-weekly) in combination with nivolumab, demonstrating maintained efficacy with fewer grade 3–4 adverse events [49]. Emerging bispecific CTLA-4/PD-1 antibodies such as MEDI5752 co-engage both checkpoints on one molecule, producing ORRs comparable to dual-antibody regimens while allowing dose optimization to manage hepatotoxicity and high-grade immune-related toxicities [19,65].

Mechanistic studies reveal that CTLA-4 competes with CD28 for CD80/86 on antigen-presenting cells (APCs), shifting the regulatory T cells (Tregs)/effector balance; probodies and tumor-restricted bispecific constructs aim to preserve effector activation while limiting Treg expansion and off-target effects [18,66,67].

Biomarkers such as tumor mutational burden (TMB ≥ 10 mutations/Mb) predict greater responses to nivolumab + ipilimumab [68], and restricted T-cell receptor (TCR) clonality correlates with improved progression-free survival under PD-1/PD-L1 therapy [69].

3.2 Adoptive Cell Therapies

3.2.1 CAR-T Cell Therapy

Chimeric antigen receptor T-cell (CAR-T) therapy and tumor-infiltrating lymphocyte (TIL) therapy harness adoptively transferred T cells to overcome RCC's immunosuppressive barriers. CAR-T cells are engineered to target tumor-associated antigens, while TIL therapy expands endogenous tumor-reactive lymphocytes for reinfusion. Both approaches have shown proof-of-concept efficacy in RCC, but face challenges from antigen heterogeneity, on-target off-tumor toxicity, and the hostile tumor microenvironment.

Early-phase trials of CD70- and CAIX-targeted CAR-T cells demonstrated manageable safety and encouraging antitumor activity in relapsed/refractory ccRCC. The CTX130 allogeneic CD70-CAR-T product achieved an 81.3% disease control rate with no dose-limiting toxicities and one durable complete response at three years [70,71]. Preclinical CD70-CAR-T cells selectively eliminated $CD70^+$ tumor cells, suggesting low off-tumor effects [72]. Affinity-tuned anti-carbonic anhydrase IX (CAIX) G9, CAR-T cells activated only at tumor-level antigen densities, yielding superior efficacy and reduced on-target off-tumor toxicity versus high-affinity counterparts in orthotopic models [73].

Next-generation "armored" CARs express a dominant-negative TGF-β receptor, resisting TGF-β–mediated suppression and driving complete remissions in xenografts [74]. Dual-antigen CAR constructs require simultaneous recognition of two tumor antigens to fire, mitigating antigen escape and off-tumor activation [75]. Combining CAR-T with checkpoint blockade enhances intratumoral persistence: PD-L1–secreting CAR-T cells outperformed conventional CAR-T in orthotopic RCC models [76], and co-administration of sunitinib improved CAR-T trafficking, proliferation, and tumor infiltration by modulating stromal and vascular barriers [77].

3.2.2 Tumor-Infiltrating Lymphocyte Therapy

TIL therapy involves isolating and expanding tumor-resident lymphocytes before reinfusion. Optimization of manufacturing has focused on subset selection and depletion of suppressive elements. Selection of TIM-3^hi/PD-1^lo subsets enabled successful expansion in 8 of 11 RCC specimens with functional profiles matching melanoma TIL products [78,79]. Pre-expansion adherent-cell depletion reduced immunosuppressive elements and enhanced TIL yield and tumor reactivity, evidenced by increased IFN-γ release upon autologous tumor challenge [80].

Genetic and cytokine engineering further boost TIL potency. CRISPR/Cas9-mediated SOCS1 knockout in TILs increased central memory formation, responsiveness to cytokines, and antitumor activity in murine RCC models [81]. TILs co-expressing IL-12 resisted tumor microenvironment (TME) suppression and demonstrated superior tumor control [82].

Clinical strategies pairing TIL infusion with checkpoint blockade have improved engraftment and efficacy. A

multicancer ACT trial combining TILs with ipilimumab/nivolumab achieved 97% expansion success and objective tumor regressions, including RCC patients [83]. Neoadjuvant nivolumab prior to nephrectomy enriched intratumoral TIL densities and was well tolerated, laying groundwork for enhanced post-surgical TIL therapy [84].

3.3 Bispecific and Multi-specific Antibody Constructs

3.3.1 Bispecific T-Cell Engagers and Related Constructs

Bispecific T-cell engagers (BiTEs) link CD3 on T cells with tumor antigens, redirecting cytotoxic T cells to eliminate cancer cells. Blinatumomab, the prototypical CD19×CD3 BiTE, has now entered RCC trials; resistance mechanisms and adverse events—particularly cytokine release syndrome (CRS)—remain challenges [85,86]. Ongoing efforts focus on format-tuning and combination regimens to maximize safety and potency [87].

Early-phase evaluations of RCC-targeted BiTE modalities highlight encouraging safety and pharmacokinetics. An ENPP3-directed antibody-drug conjugate (AGS16F) was well tolerated in phase I trials, with effective tumor localization and active metabolite formation translating into significant tumor control in RCC xenografts [88].

For CAIX×CD3 BiTEs, a "persistent multivalent T-cell engager" (PMTE) delivered via synthetic DNA (synDNA) exhibited a 40-fold increase in cytotoxic potency and a favorable 4-day half-life in murine models versus the 2-hour half-life of first-generation BiTE proteins [87].

Next-generation multispecific constructs co-engage CD3, tumor antigen, and costimulator, yielding superior activation and tumor control in preclinical models [89]. Format and affinity adjustments create a "cytokine window," decoupling tumor killing from CRS [90,91].

Table 2 provides a side-by-side comparison of all major immunotherapeutic modalities in RCC, highlighting their mechanisms, clinical stage, advantages and limitations.

Table 2. Comparative Immunotherapeutic Modalities in RCC

	Modality	Mechanism of Action	Clinical Phase	Advantages	Limitations
1	Immune Checkpoint Inhibitors (ICI)	Block PD-1/PD-L1 or CTLA-4 to reverse T-cell exhaustion	Approved (Phase III data)	Durable responses; broad approval	Immune-related AEs; primary resistance
2	CAR-T (CAIX-targeted)	Engineered T cells recognizing CAIX antigen	Phase I/II	Targeted cytotoxicity	Off-tumor toxicity; limited persistence
3	BiTEs (CD3-CAIX)	Bispecific engager linking T cells to tumor cells via CD3 and CAIX	Preclinical/ Phase I	Potent T-cell activation	Cytokine release syndrome; early development
4	Tumor Vaccines	Induce antigen-specific T-cell responses via peptide/DC/neoantigen	Phase I–III	Antigen-specific; low systemic toxicity	Limited efficacy; complex manufacture

3.4 Tumor Vaccines

Tumor vaccines aim to stimulate robust, antigen-specific immune responses by delivering cancer antigens via DNA, RNA, peptide, or viral vectors to antigen-presenting cells (APCs), which in turn activate $CD8^+$ T cells and, through $CD4^+$ help, B-cell antibody production [92]. Personalized neoantigen vaccines—designed from individual tumor mutations—minimize central tolerance and have demonstrated tumor regression and durable recurrence-free survival in early studies [93,94].

3.4.1 Platforms & Clinical Data

Phase I trials in resected high-risk ccRCC (NCT02950766) using peptide-based personalized cancer vaccines reported no recurrences at a median 40.2 months follow-up, with all patients mounting durable T-cell responses against driver neoantigens [95]. A heterologous chimpanzee adenovirus (ChAd68) prime/self-amplifying mRNA boost vaccine combined with nivolumab/ipilimumab induced lasting neoantigen-specific $CD8^+$ T-cell expansions in advanced RCC [96]. NOUS-PEV, a polyvalent Great Ape Adenoviral/ Modified Vaccinia Ankara [MVA] vector expressing 60 neoantigens alongside pembrolizumab, drove rapid T-cell receptor clonotype diversification and potent antitumor immunity in a phase I setting [97].

Therapeutic vaccines for RCC differ fundamentally in how antigens are delivered, personalized, and presented to the immune system. IMA901, a multi-peptide vaccine composed of tumor-associated peptides identified from RCC specimens, elicits broad $CD8^+$ and $CD4^+$ T-cell responses; in clinical studies, the breadth of multi-peptide responses—and concurrent reduction in regulatory T cells—correlated with longer survival in metastatic RCC [98–100]. AGS-003, an autologous dendritic-cell vaccine loaded ex vivo with amplified

tumor RNA and synthetic CD40L RNA, drives robust expansion of effector-memory $CD8^+$ T cells; when combined with sunitinib, AGS-003 achieved a 33 percent five-year survival rate in intermediate/poor-risk patients, with memory T-cell increases directly linked to overall survival [101]. Neoantigen vaccines leverage next-generation sequencing to identify patient-specific mutations (e.g., VHL, PBRM1) and encode these neoepitopes as peptides or RNA; in the adjuvant trial NCT02950766, such vaccines induced durable $CD8^+$ memory and maintained 100 percent recurrence-free status at 40 months [95,102]. DNA/RNA platforms, which encode antigens in situ to enable endogenous major histocompatibility complex (MHC) I/II presentation, offer rapid, scalable manufacturing and have shown enhanced polyfunctional $CD8^+$ T-cell activation and favorable safety when combined with checkpoint blockade [102–104].

Advanced proteogenomic pipelines such as NeoDisc integrate immunopeptidomics with genomic and transcriptomic data to prioritize truly immunogenic neoantigens [105]. Cross-cohort analyses of TCGA and International Cancer Genome Consortium (ICGC) datasets further inform mRNA vaccine antigen selection and patient stratification [106].

3.4.2 Post-Nephrectomy Vaccines

In the adjuvant setting following nephrectomy, vaccines offer the promise of eradicating minimal residual disease and preventing recurrence. Personalized peptide and neoantigen vaccines administered post-surgery have generated strong, durable $CD4^+$ and $CD8^+$ T-cell memory—with zero recurrences at 40 months in NCT02950766—highlighting their potential to sustain long-term tumor control [95]. Looking forward, combining these vaccines with immune checkpoint inhibitors may overcome tumor-mediated immunosuppression and amplify vaccine-induced T-cell expansion; circulating biomarkers such as ctDNA dynamics and TCR clonality are being explored for early relapse detection and real-time monitoring of vaccine efficacy [107,108]. Optimizing vaccination schedules based on immune-pharmacodynamic readouts—peripheral T-cell expansion, cytokine profiles, and ctDNA clearance—represents a rational strategy to maximize benefit and minimize unnecessary treatment.

Table 3 summarizes the vaccine platforms under investigation in RCC, their antigenic targets, immune-cell focus, relevant mutations/antigens and key supporting evidence.

Table 3. RCC Vaccine Strategies

	Vaccine Strategy	Target/Neoantigen	Immune Target	Relevant Mutations/Antigens	Evidence
1	IMA901 (multipeptide)	Nine tumor-associated peptides	T cells	TUMAPs from 9 antigens	Phase II: no OS benefit added to sunitinib; immune responses correlated with OS
2	AGS-003 (autologous DC)	Patient tumor RNA (including VHL, MET transcripts)	APCs (dendritic cells) & T cells	Multiple transcripts incl. VHL	Phase II: extended median and long-term survival with sunitinib; well tolerated
3	Rocapuldencel-T (ADAPT)	Patient tumor RNA (autologous DC)	APCs (dendritic cells) & T cells	Patient-specific whole tumor transcriptome	Phase III ADAPT ongoing: OS endpoint; interim OS data awaited
4	Personalized Neoantigen PCV	Patient-specific predicted neoantigens	T cells	Somatic missense mutations	Phase I: 9/9 no recurrence at 40 mo; safe, no DLTs

4. Combined Immunotherapy

As shown in Figure 2, six complementary T cell–targeting strategies form the basis for our combination approaches.

Figure 2 summarizes six major strategies for harnessing T cells against cancer: (1) Immune Checkpoint Inhibitors block inhibitory receptors (PD-1, CTLA-4) or ligands (PD-L1) to reverse T-cell exhaustion; (2) Adoptive Cell Therapies reinfuse tumor-reactive lymphocytes—either patient-derived TILs or genetically engineered Chimeric antigen receptor T cell (CAR-T)—to achieve direct cytotoxicity; (3) Cytokine Therapy delivers pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ) to expand and activate effector T cells; (4)Tumor Vaccines present tumor antigens via MHC on dendritic cells or peptide platforms to prime naïve T cells through the TCR; (5) Bispecific T-Cell Engagers physically link CD3 on T cells to tumor antigens (e.g. bispecific antibodies) to redirect cytotoxicity; (6) Chemokine-Based Approaches exploit chemokine–receptor pairs (e.g. C-X-C motif chemokine ligand [CXCL] 10 to C-X-C motif chemokine receptor [CXCR] 3) to enhance T-cell trafficking into the tumor microenvironment.

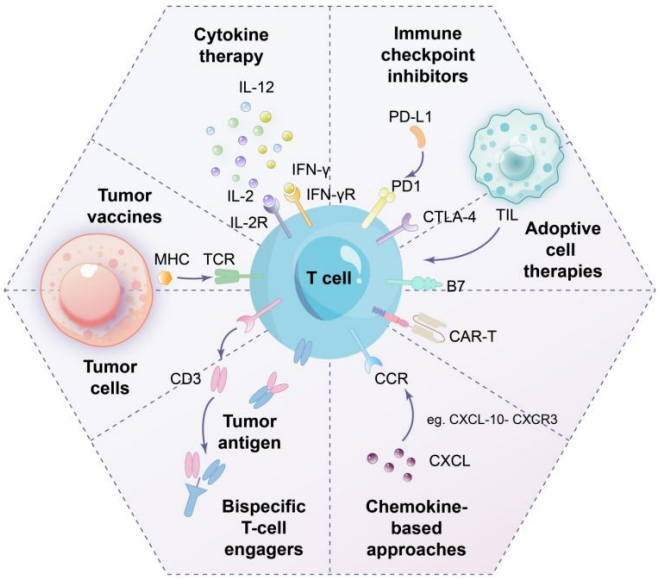

Figure 2. Overview of T Cell–Directed Immunotherapeutic Modalities

4.1 Research on Immune Checkpoint Inhibitor Combinations (e.g., PD-1/CTLA-4 Combination Therapy)

The simultaneous inhibition of two nonredundant immune checkpoints can amplify T-cell activation and tumor cell eradication compared with monotherapy, but at the cost of increased immune-related toxicity. In renal cell carcinoma (RCC), the combination of ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) has demonstrated superior efficacy over PD-1 blockade alone, yielding a median progression-free survival (PFS) of 4 months and objective response rates exceeding 40% [109,110]. The alignment of these combination regimens with specific RCC molecular subtypes and predictive biomarkers is illustrated in Figure 3.

Emerging dual-checkpoint strategies targeting PD-1 with LAG-3 or TIGIT have shown promising activity. Pembrolizumab plus favezelimab (anti-LAG-3) produced response rates similar to other dual regimens with manageable toxicity profiles [111,112], while PD-1/TIGIT co-blockade achieved enhanced antitumor activity in PD-1/VEGF-TKI-refractory patients, restoring CD226-mediated cytotoxicity [113–115].

Figure 3 links four major therapeutic strategies—(1) ICI + CTLA-4 blockade, (2) ICI + VEGF-TKI (annotated with high angiogenesis signatures), (3) ICI + radiation or surgery, and (4) emerging regimens (PARP-inhibitor (PARPi) + ICI, dual TIGIT/PD-1 blockade, bispecific T-cell engagers)—to three immunogenomic subtypes (Immunity-High, M3 [immune-inflamed, metabolic-desert], Immunity-Low/M2) via their associated biomarkers (PD-L1, TIGIT/TMB, angiogenesis gene signatures). Arrows indicate which combinations are predicted to yield the greatest clinical benefit for each biomarker-defined subgroup.

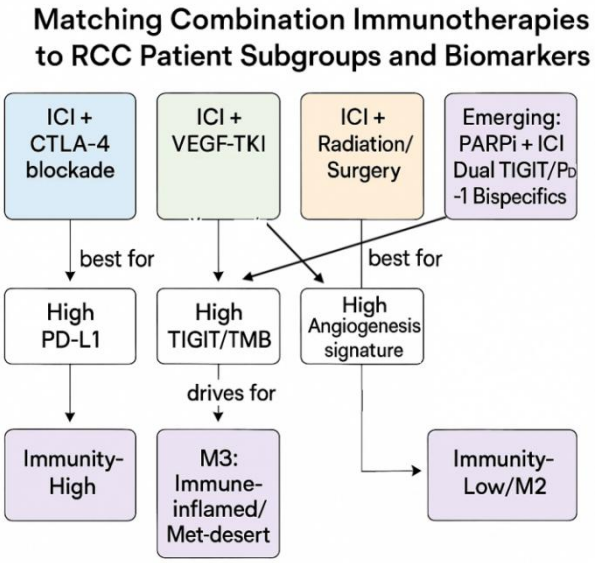

Figure 3. Matching Combination Immunotherapies to RCC Patient Subgroups and Biomarkers.

4.1.1 Biomarker-Driven Patient Stratification and Clinical Integration

High TIGIT expression in advanced RCC correlates with poor prognosis, immune-exhaustion signatures, and enhanced response to anti-PD-1 therapy. TIGIT is frequently co-expressed with PD-1, and its upregulation identifies patients likely to benefit from dual PD-1/TIGIT blockade or bispecific antibodies [115–119].

Angiogenesis-related gene signatures (e.g., VEGF, T-effector, and mixed profiles) stratify tumors into subgroups that preferentially respond to VEGF-targeted plus ICI combinations. Tumors with high angiogenesis signatures demonstrate superior outcomes with atezolizumab + bevacizumab or pembrolizumab + axitinib regimens [120,121].

4.2 Combination of Immunotherapy with Traditional Therapies

4.2.1 Synergistic Effects of Immunotherapy and Targeted Therapy (e.g., VEGF Inhibitors)

Combining immune checkpoint inhibitors (ICIs) with VEGF-targeted therapies normalizes tumor vasculature, alleviates immunosuppression, and enhances immune cell infiltration. In IMmotion151, atezolizumab plus bevacizumab improved median PFS to 11.2 months versus 7.7 months with sunitinib in first-line metastatic RCC (HR 0.74, $p = 0.0217$) [122]. Similar benefits have been observed with pembrolizumab plus axitinib and nivolumab plus cabozantinib, both showing superior overall survival and response rates compared with monotherapy [123].

VEGF blockade shifts the tumor microenvironment toward immunostimulatory phenotypes: it increases intratumoral $CD8^+$ T-cell density, enhances MHC-I and Th1 cytokine expression, and reduces regulatory T cells and myeloid-derived suppressor cells [124,125]. Elevated baseline and on-treatment $CD8^+$ infiltration, upregulated adhesion molecules (e.g., ICAM-1), and dynamic changes in circulating VEGF-A levels serve as predictive biomarkers for ICI + TKI benefit [126,127].

4.2.2 Combined Strategies with Radiotherapy and Surgical Treatments

Radiotherapy induces immunogenic cell death, releasing tumor antigens and promoting dendritic-cell activation. In the RAPPORT trial of SABR plus pembrolizumab for oligometastatic RCC, 2-year PFS was 45% with a 92% local control rate and no grade 4–5 toxicities, suggesting potential abscopal effects [128,129]. Preclinical work supports hypofractionated regimens (e.g., 8 Gy × 3) as optimal for maximizing immune priming while maintaining safety [130,131].

Perioperative immunotherapy integrated with nephrectomy also shows promise. Neoadjuvant nivolumab before surgery in locally advanced clear-cell RCC was feasible and enriched intratumoral lymphocytes without surgical delays [84,132]. Adjuvant pembrolizumab post-nephrectomy improved 24-month disease-free survival (77.3% vs 68.1% placebo) in high-risk patients [133]. Optimal sequencing—neoadjuvant versus adjuvant—remains under study, with data suggesting preoperative immune priming may yield superior long-term control [134,135].

4.2.3 Combination of Immunotherapy with Emerging Therapies

The convergence of DNA damage response inhibitors and metabolic modulators with immune checkpoint blockade offers a novel paradigm to surmount resistance in renal cell carcinoma (RCC). PARP inhibitors exploit homologous recombination deficiencies to increase tumor mutational burden and neoantigen release, potentiating T-cell–mediated immunity. Meanwhile, targeting metabolic checkpoints—such as the adenosinergic axis, tryptophan catabolism, glutamine dependency, and hypoxia pathways—can alleviate immunosuppressive biochemical barriers, reinvigorating tumor-infiltrating lymphocytes (TILs) and enhancing responsiveness to PD-1/PD-L1 inhibitors.

PARP inhibitors combined with PD-1/PD-L1 blockade have shown encouraging signals in HR-deficient RCC subgroups. The ORCHID trial (NCT03786796) of olaparib in BAP1-mutant or other DNA repair–deficient metastatic RCC reports a six-month disease control rate endpoint [136]. Similarly, talazoparib plus avelumab in VHL-alteraigan1ed and DNA repair–deficient advanced RCC yields improved objective response rates and PFS versus historical controls [137]. Mechanistically, PARP inhibition amplifies genomic instability, upregulates PD-L1, activates type I interferon pathways, and fosters antigen presentation—synergies confirmed by preclinical studies and clinical observations [138–143].

Adenosinergic immunosuppression is another key metabolic resistance node in RCC. CD73 generates extracellular adenosine, which via A2A receptor signaling dampens effector T-cell activity. Preclinical blockade of CD73 or A2A receptor enhances T-cell–dependent tumor control and synergizes with PD-1/PD-L1 inhibitors [144–148]. In a phase I study, the A2A antagonist ciforadenant was well tolerated in treatment-refractory RCC, induced $CD8^+$ T-cell infiltration, broadened the T-cell repertoire, and achieved durable disease control, including responses after prior PD-1/PD-L1 failure [149].

Other metabolic targets also modulate TIL function and ICI efficacy. IDO1 inhibitors reverse tryptophan depletion and kynurenine accumulation, restoring effector T-cell proliferation and reducing regulatory T-cell suppression; combination with PD-1 blockade enhances antitumor immunity in preclinical RCC models [9,150]. Glutaminase inhibitors disrupt tumor glutamine metabolism, impairing tumor growth while reprogramming the microenvironment to favor T-cell activity and synergizing with ICIs [149,150].

Finally, hypoxia in RCC fosters immune escape via HIF-2α–driven transcription. HIF-2α inhibitors such as belzutifan, when combined with ICIs, remodel the TME by reducing angiogenesis and immunosuppressive factor expression, converting “cold” tumors to “hot” and overcoming prior ICI resistance [9,151,152].

5. Challenges of Immunotherapies

In this section, we review key barriers to effective immunotherapy in RCC, including both intrinsic and acquired resistance mechanisms, the challenges of implementing multi-layer biomarker strategies in routine practice, and the trade-offs between tissue-based (Immunohistochemistry, IHC) and liquid-biopsy (ctDNA) platforms in terms of cost, feasibility, and turnaround time. We also introduce a schematic (Figure 4) depicting metabolic crosstalk between immune cells and cancer-associated fibroblasts (CAFs) that underlies therapeutic resistance.

Figure 4 reflects the interactions described by Sahai E et al. [153]: CAFs perform heightened glycolysis, exporting lactate that acidifies the microenvironment and shifts T-cell metabolism, while also mediating amino-acid exchange (alanine/aspartate shuttling) and depleting essential amino acids. CAFs' secreted factors—TGF-β, IL-6, CXCL12, C-C motif chemokine ligand 2 (CCL2), adenosine, and IDO/kynurenine—further suppress T-cell bioenergetics. These combined stresses converge on metabolic exhaustion and functional suppression of T cells, reinforcing a resistant, immune-cold (M2-like) phenotype.

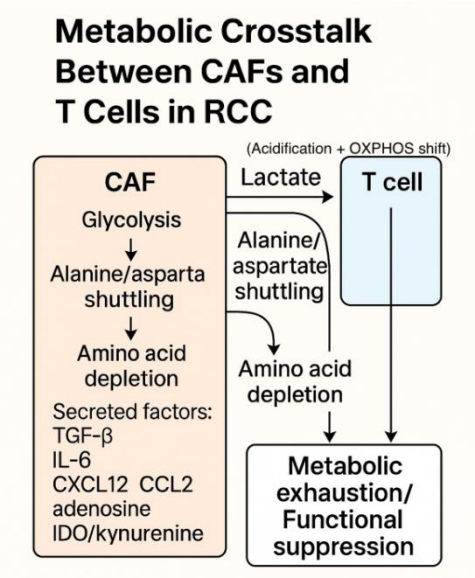

Figure 4. Metabolic Crosstalk Between CAFs and T Cells in RCC

5.1 Mechanisms of Treatment Resistance

Despite the transformative impact of immune checkpoint inhibitors (ICIs) in RCC, both intrinsic and acquired resistance severely limit durable responses. Intrinsic resistance often reflects the tumor's baseline genetic and epigenetic features—such as low MHC class I expression due to β2-microglobulin loss—which impair antigen presentation and T-cell recognition [154,155]. Tumors may also harbor an enhancer demethylator phenotype driven by TET1 promoter hypomethylation, activating IL6/JAK/STAT3 signaling and fostering an immunosuppressive microenvironment resistant to ICIs [24].

Acquired resistance emerges under therapeutic pressure: longitudinal ctDNA and paired biopsy analyses reveal new escape alterations, including β2-microglobulin (B2M) loss, HLA loss-of-heterozygosity, CDKN2A/B deletion, and upregulation of alternative checkpoints (TIM-3, LAG-3, TIGIT) on tumor-infiltrating lymphocytes [117,156]. Such adaptations coincide with intra-tumoral heterogeneity and neoantigen depletion, further enabling immune escape [155,156].

Moreover, the tumor microenvironment (TME) itself—including hypoxia, TGF-β, IL-10, regulatory T cells, and myeloid-derived suppressor cells—reinforces resistance by dampening effector T-cell function and promoting suppressive cell populations [157–159].

5.2 Immunosuppressive Effects of the Tumor Microenvironment

The RCC TME orchestrates potent immunosuppression. Soluble factors such as TGF-β inhibit T-cell activation and foster regulatory T-cell differentiation, while IL-10 further suppresses effector responses [160,161]. Hypoxia and adenosine accumulation—via CD73 and A2A receptor signaling—attenuate cytotoxic T-cell activity, a pathway whose blockade reinvigorates antitumor immunity [145,162].

Stromal elements exacerbate this milieu: cancer-associated fibroblasts (CAFs) secrete CXCL12 and remodel the extracellular matrix, physically excluding T cells [163,164]. Subset-specific CAF targeting (e.g., NOX4 inhibition, CXCR4 blockade, synthetic retinoids) normalizes stroma and synergizes with ICIs to promote T-cell infiltration [165,166]. Tumor-associated macrophages, particularly M2-like TAMs, propagate suppression via IL-10, TGF-β, and PD-L1; reprogramming or depleting TAMs (colony-stimulating factor 1 receptor [CSF-1R] inhibition, IL-1β blockade, cytokine-engineered macrophages) restores antitumor immunity [167,168].

Angiogenesis-independent vascular normalization—through angiopoietin-2 (ANG2) inhibition (e.g., trebananib) or dual ANG2/VEGFA blockade—also enhances immune cell extravasation and antitumor responses, especially when combined with PD-1 blockade [169,170].

5.3 Screening of Biomarkers and Efficacy Prediction

Accurate biomarkers are indispensable for tailoring immunotherapy in RCC. Traditional markers—tumor mutational burden (TMB), PD-L1 expression, and T-effector gene signatures—offer prognostic insights but lack sufficient predictive power when used in isolation [171–173].

Multimodal panels integrating PD-L1 IHC, TMB, T-effector signatures, and ctDNA dynamics improve predictive accuracy. High baseline ctDNA and lack of ctDNA clearance correlate with poor outcomes, whereas early ctDNA negativity forecasts durable responses [108,174,175].

Digital pathology and AI-driven spatial analysis further refine biomarker assessment by quantifying immune-cell architecture—mapping HLA-neoantigen landscapes and T-cell/TAM interactions to predict ICI benefit [176–178].

Host factors, notably HLA genotype diversity (HLA-B evolutionary divergence) and germline polymorphisms, augment tumor-centric markers, with higher HLA divergence linked to enhanced T-cell infiltration and improved ICI responses when combined with lenvatinib/pembrolizumab [179,180].

Building on our analysis of intrinsic and acquired resistance and the integration of diverse biomarker modalities, the following section examines the practical and economic challenges of implementing tissue-based immunohistochemistry versus liquid-biopsy approaches in RCC management.

5.4 Feasibility and Cost of Multivariate Biomarker Platforms in Clinical Practice

Immunohistochemistry (IHC) is a feasible and cost-effective platform for biomarker assessment in advanced RCC, particularly for tissue-based markers such as TIGIT expression and angiogenesis-related gene signatures. It is widely available in pathology laboratories, requires minimal specialized equipment, and can be performed on standard formalin-fixed paraffin-embedded tissue. IHC is well-suited for single or limited multiplex marker analysis, but its scalability and ability to capture complex multigene signatures are limited, and inter-assay variability and subjective interpretation can affect reproducibility—especially for emerging markers like TIGIT [120,181–184].

Circulating tumor DNA (ctDNA) analysis offers a minimally invasive, repeatable approach for dynamic monitoring of tumor genomics and response to therapy, but its implementation in RCC faces both feasibility and cost challenges. ctDNA assays require advanced sequencing infrastructure, are more expensive than IHC, and have variable sensitivity in RCC due to low tumor DNA shedding, particularly in indolent or low-burden disease. However, ctDNA can complement tissue profiling by capturing tumor heterogeneity and temporal evolution, and may be particularly useful for monitoring angiogenesis-related gene signatures and resistance mechanisms [185–187].

Integration of multivariate biomarker platforms in clinical practice for advanced RCC is currently limited by cost, assay standardization, and the need for prospective validation of clinical utility for patient stratification and immunotherapy response prediction [120,187–189]. Combining IHC for TIGIT and tissue-based gene signatures with ctDNA analysis may provide complementary information, but widespread adoption will depend on further evidence of clinical benefit and cost-effectiveness [186,187].

5.5 Future Prospects

Despite the transformative impact of immunotherapy in renal cell carcinoma, several limitations constrain its broader success. First, both primary and acquired resistance limit durable responses: tumors can evade immune attack through impaired antigen presentation, activation of alternative inhibitory pathways, and adaptive rewiring of the microenvironment. Second, the complex and heterogeneous tumor microenvironment—including areas of hypoxia, metabolic suppression, and dense stromal barriers—impedes effective infiltration and function of effector lymphocytes. Third, the absence of widely validated predictive biomarkers hampers the ability to tailor therapies; existing markers provide only partial guidance, and many patients still undergo ineffective or toxic treatments. Fourth, advanced cellular therapies and engineered biologics face practical challenges of manufacturing complexity, cost, and on-target off-tumor toxicity.

Looking ahead, overcoming these hurdles will require integrated strategies. Rational combination regimens that simultaneously target checkpoints, metabolic and hypoxia pathways, and vascular normalization hold promise for reversing resistance and converting immune-cold tumors into immune-hot ones. Vaccine-adjuvant and delivery innovations—such as STING agonist co-formulations with oncolytic HSV-1 or NanoSTING-vax—can further prime T cells and remodel suppressive myeloid niches.

Tumor-Infiltrating Lymphocyte (TIL) Therapy: Recent RCC-specific TIL trials have confirmed the feasibility of ex vivo expansion using second-generation protocols, with expansion success correlating to a high intratumoral $CD8^+/FoxP3^+$ ratio and low PD-1 expression on Tregs. Nonetheless, reliably generating highly tumor-reactive TILs remains challenging due to antigen heterogeneity and selection of optimal neoantigen-specific clones. Advances in single-cell sequencing and CRISPR editing are being explored to enrich for polyfunctional, tumor-specific TIL populations, but robust in vivo persistence and function in the immunosuppressive RCC microenvironment are still under investigation [79,82].

CAR-T Cell Therapy: The most advanced RCC trials target CD70, highly expressed in clear-cell and sarcomatoid variants. The allogeneic CD70 CAR-T product CTX130 achieved disease control in a majority of patients and one durable complete response, validating proof-of-concept in RCC. Key barriers include ensuring tumor specificity to avoid off-tumor toxicity, scaling manufacturing of allogeneic/off-the-shelf products, and enhancing CAR-T infiltration and persistence

within the stroma-rich, hypoxic RCC milieu. Engineering solutions—chemokine receptor modification to direct homing, multi-antigen constructs to mitigate antigen escape, and "armored" CARs secreting cytokines—are in early trials to overcome these obstacles [71,190–192].

We summarize these multilayered interventions in Figure 5, which provides a roadmap for next-generation RCC immunotherapy trials. Continued development of high-resolution biomarkers—leveraging spatial transcriptomics, ctDNA dynamics, and TCR clonality—will enable real-time, patient-specific monitoring and adaptive treatment adjustments. Advances in cellular engineering (armored/multi-antigen CAR-T and gene-edited TILs) and convergence of systems biology with advanced imaging and computational modeling will guide precision immunotherapy, matching each RCC tumor's unique features with optimal vaccine, checkpoint, and cell-based combinations.

Figure 5 synthesizes four interlocking approaches—checkpoint inhibitors, vaccine/adjuvant platforms, TIL and CAR-T cell engineering, and biomarker-driven adaptation—around the central challenge of RCC immunotherapy resistance, providing a roadmap for future clinical development.

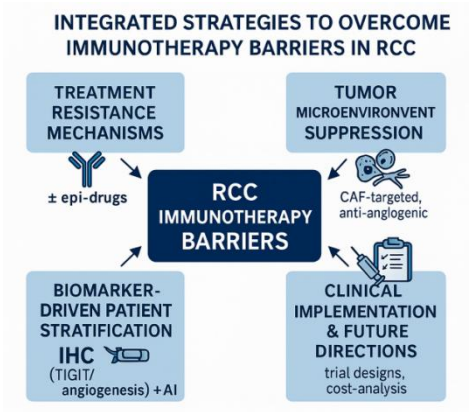

Figure 5. Integrated Strategies to Overcome Immunotherapy Barriers in RCC

6. Conclusion

Immunotherapy has transformed the treatment paradigm of RCC, achieving durable remissions in a subset of patients who previously faced limited options. However, persistent challenges—including therapeutic resistance, TME-mediated immunosuppression, and the need for precise biomarkers—must be addressed to extend these benefits to a broader patient population. Ongoing translational research and early-phase trials are exploring multifaceted combination strategies that target complementary pathways, reshape the tumor microenvironment, and harness advanced cellular and molecular technologies. By integrating insights from single-cell profiling, proteogenomics, digital pathology, and host-tumor genomics, future approaches will enable personalized, adaptive immunotherapy regimens. Continued collaboration between basic, translational, and clinical investigators is essential to overcome current limitations and realize the full potential of immunotherapy in RCC.

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