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Evolution of Systemic Therapy in Metastatic Renal Cell Carcinoma: From Cytokines to Immune Checkpoint Inhibitors and HIF-2α Targeted Therapy

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Abstract: ***Metastatic renal cell carcinoma (mRCC) has undergone a remarkable therapeutic transformation over the past three decades. Initially, treatment relied on cytokine-based immunotherapy with interferon-alpha (IFN-α) and high-dose interleukin-2 (HD IL-2), which produced durable responses in a small subset of patients but were associated with substantial toxicity. Advances in understanding the molecular biology of clear-cell renal cell carcinoma (ccRCC), particularly the role of von Hippel-Lindau (VHL) gene inactivation and hypoxia-inducible factor (HIF) signaling, led to the development of vascular endothelial growth factor (VEGF)-targeted therapies and mammalian target of rapamycin (mTOR) inhibitors. Although these agents significantly improved progression-free survival, durable complete responses remained uncommon. The advent of immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) revolutionized the management of mRCC and now forms the foundation of contemporary treatment. Landmark clinical trials including CheckMate 025, CheckMate 214, KEYNOTE-426, CheckMate 9ER, and CLEAR have demonstrated significant improvements in survival and durable disease control. More recently, HIF-2α inhibition with belzutifan has emerged as a novel therapeutic strategy directly targeting the molecular drivers of ccRCC. This review summarizes the evolution of systemic therapy in RCC, emphasizing immune checkpoint blockade, immunotherapy-based combinations, emerging therapeutic approaches, and future directions in precision immuno-oncology (1-10).***

Keywords: Renal cell carcinoma; metastatic renal cell carcinoma; immune checkpoint inhibitors; immunotherapy; PD-1; CTLA-4; belzutifan; HIF-2α

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 90% of all primary renal malignancies and remains one of the most lethal urological cancers worldwide. Clear-cell renal cell carcinoma (ccRCC), the predominant histological subtype, constitutes approximately 70–80% of all RCC cases and is characterized by distinctive molecular and immunological features that have shaped modern therapeutic development (1-5).

Despite improvements in diagnostic imaging and surgical management, approximately 20–30% of patients present with metastatic disease at diagnosis, while a substantial proportion develop recurrence following definitive treatment of localized tumors. Historically, metastatic RCC was associated with poor outcomes because of intrinsic resistance to conventional chemotherapy and radiotherapy. Before the development of targeted therapies and immunotherapy, median overall survival rarely exceeded one year (2-5).

The therapeutic landscape of RCC has evolved dramatically over the past three decades. Initial treatment strategies relied on cytokine-based immunotherapy, followed by the introduction of VEGF-targeted therapies and mTOR inhibitors. More recently, immune checkpoint inhibitors have transformed clinical practice, producing unprecedented improvements in overall survival, progression-free survival, and durable response rates. The emergence of HIF-2α inhibitors and next-generation immunotherapeutic approaches continues to redefine the management of advanced RCC (6-10).

Immunobiology of RCC and Rationale for Immunotherapy

Renal cell carcinoma is among the most immunogenic solid tumors and possesses a complex tumor microenvironment rich in immune cells, inflammatory mediators, and angiogenic factors. The presence of tumor-infiltrating lymphocytes, spontaneous tumor regression in rare cases, and responsiveness to cytokine therapy historically suggested an important role for host immunity in disease control (7-10).

Immune responses against tumor cells are regulated through a dynamic balance between stimulatory and inhibitory pathways. Among the most important inhibitory pathways are CTLA-4 and PD-1/PD-L1. CTLA-4 primarily regulates early T-cell activation within lymphoid tissues by competing with CD28 for binding to CD80 and CD86 on antigen-presenting cells. PD-1 functions predominantly within peripheral tissues and the tumor microenvironment, where interaction with PD-L1 suppresses T-cell proliferation, cytokine secretion, and cytotoxic activity, ultimately leading to T-cell exhaustion (8, 9).

Many RCC tumors express PD-L1 and exploit these checkpoint pathways to evade immune surveillance. Increased PD-L1 expression has been associated with aggressive tumor biology, adverse pathological features, and inferior clinical outcomes. Blockade of PD-1, PD-L1, or

CTLA-4 restores antitumor immunity and forms the biological basis for modern immune checkpoint inhibition (8-10).

Another defining characteristic of ccRCC is dysregulation of angiogenesis. Inactivation of the VHL tumor suppressor gene results in stabilization of hypoxia-inducible factors (HIF-1α and HIF-2α), leading to overexpression of VEGF and other proangiogenic mediators. Beyond promoting angiogenesis, VEGF exerts profound immunosuppressive effects by impairing dendritic-cell maturation, reducing antigen presentation, promoting regulatory T-cell expansion, and limiting cytotoxic T-cell infiltration. These observations provided the biological rationale for combining VEGF-targeted therapy with immune checkpoint blockade, a strategy that now represents a cornerstone of first-line treatment in advanced RCC (5,6,10).

Evolution of Systemic Therapy in RCC

Cytokine Era

The first effective systemic therapies for metastatic RCC were cytokine-based agents, primarily interferon-alpha (IFN-α) and high-dose interleukin-2 (HD IL-2). IFN-α demonstrated modest antitumor activity through enhancement of antigen presentation and activation of natural killer cells, producing objective response rates of approximately 10–15% (11,12).
HD IL-2 represented a major advance by stimulating proliferation and activation of cytotoxic T lymphocytes and natural killer cells. Clinical studies reported objective response rates of 15–20%, with complete responses observed in approximately 5–8% of patients. Importantly, a subset of complete responders achieved durable remissions lasting more than a decade, providing the first evidence that metastatic RCC could potentially be controlled through immune-mediated mechanisms (13-15).

Despite these encouraging outcomes, cytokine therapy was associated with substantial toxicity, including capillary leak syndrome, hypotension, pulmonary edema, renal dysfunction, and cardiac complications. Consequently, its use was limited to carefully selected patients treated at specialized centers (16).

Although cytokines have largely been replaced by modern therapies, they established RCC as an immunologically responsive malignancy and laid the foundation for subsequent immunotherapeutic advances.

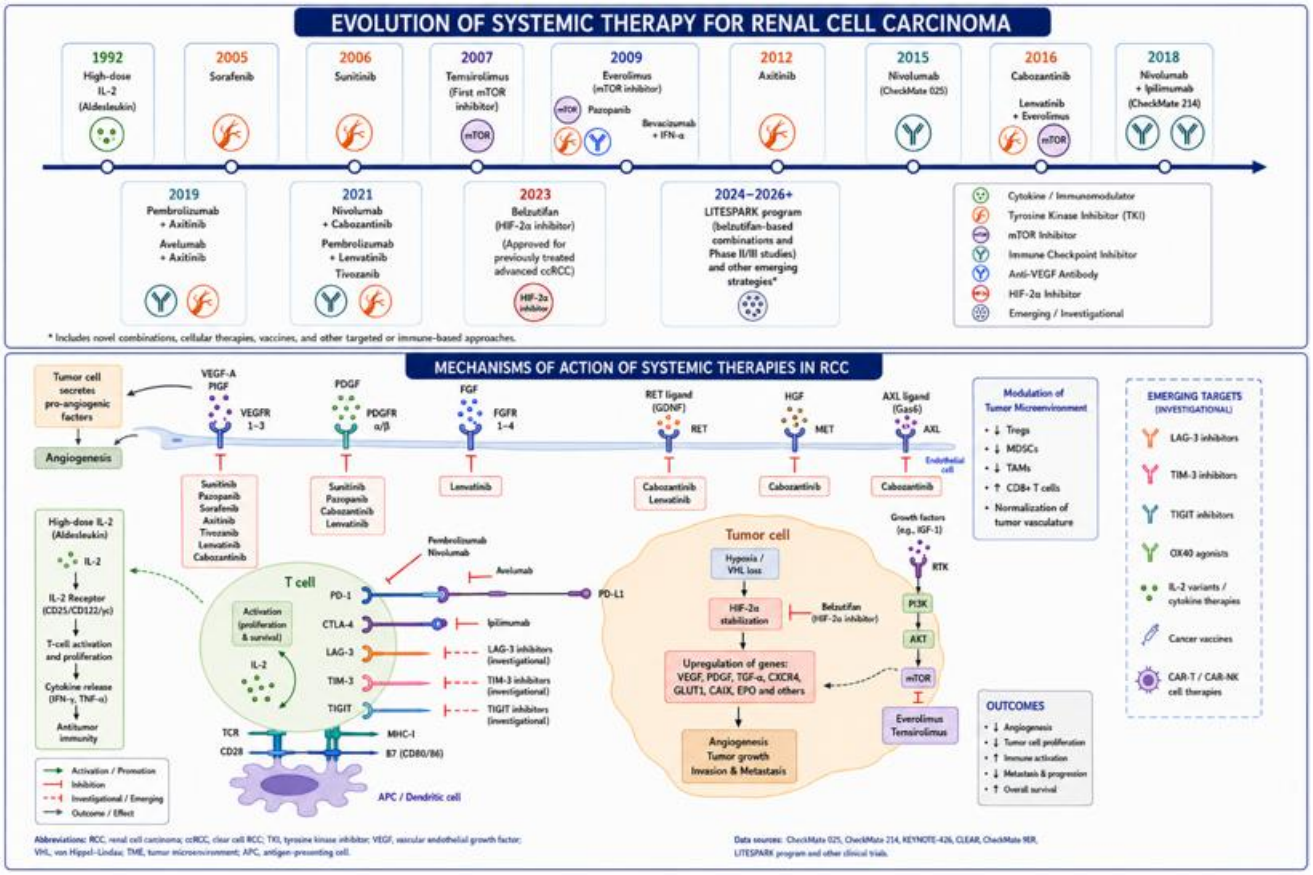
Targeted Therapy Era

The discovery of VHL gene inactivation and its central role in ccRCC pathogenesis transformed the management of advanced RCC. Loss of VHL function results in stabilization of HIF proteins and subsequent activation of VEGF-mediated angiogenesis, providing a rational therapeutic target (5,6).

This biological insight led to the development of VEGF-targeted tyrosine kinase inhibitors (TKIs), including sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib. The TARGET trial established sorafenib as an effective therapy in previously treated disease, while sunitinib subsequently demonstrated superiority over interferon-alpha and became the standard first-line treatment for advanced RCC (17,18).

Additional studies including COMPARZ and AXIS further expanded therapeutic options and refined treatment selection among VEGF-targeted agents (19,20). Simultaneously, the identification of the mammalian target of rapamycin (mTOR) pathway led to the development of temsirolimus and everolimus, which demonstrated clinical benefit in selected patient populations (21,22).

Although targeted therapies significantly improved progression-free survival and quality of life compared with cytokine therapy, durable complete responses remained uncommon and acquired resistance inevitably developed. These limitations ultimately stimulated renewed interest in immunotherapy and paved the way for the immune checkpoint inhibitor era.



Immune Checkpoint Inhibitors in Metastatic RCC

The introduction of immune checkpoint inhibitors (ICIs) marked a paradigm shift in the management of metastatic RCC. Unlike targeted therapies that primarily inhibit tumor angiogenesis, ICIs restore endogenous antitumor immunity by blocking inhibitory pathways that suppress T-cell activation and function. Monoclonal antibodies directed against PD-1, PD-L1, and CTLA-4 have demonstrated durable responses and significant survival benefits across multiple clinical settings, establishing immunotherapy as a cornerstone of modern RCC treatment (23-28).

Initially, ICI monotherapy demonstrated promising activity in patients who had progressed after VEGF-targeted therapy. Subsequently, combination approaches involving dual checkpoint blockade or PD-1 inhibitors combined with VEGF-targeted tyrosine kinase inhibitors (TKIs) produced superior outcomes and became preferred first-line treatment strategies for advanced disease.

CHECKMATE 025

The phase III CheckMate 025 trial established nivolumab as the first immune checkpoint inhibitor to demonstrate an overall survival benefit in metastatic RCC. The study enrolled 821 patients with advanced RCC who had progressed after one or more antiangiogenic therapies and randomized them to receive nivolumab or everolimus (29).

Nivolumab significantly improved median overall survival compared with everolimus (25.0 vs. 19.6 months; HR 0.73; p=0.002). Objective response rates were also superior with nivolumab (25% vs. 5%), while grade 3–4 treatment-related adverse events occurred less frequently than with everolimus (19% vs. 37%) (29). Long-term follow-up confirmed durable responses and sustained survival benefit, firmly establishing nivolumab as the standard second-line therapy for advanced RCC (30).

Checkmate 214

The CheckMate 214 trial transformed first-line treatment by evaluating nivolumab plus ipilimumab versus sunitinib in treatment-naïve advanced RCC patients (31).

Among intermediate- and poor-risk patients, nivolumab plus ipilimumab demonstrated significant improvements in overall survival, progression-free survival, and objective response rates. Initial analyses reported an objective response rate of 42% compared with 27% for sunitinib, with complete responses observed in approximately 10% of patients (31).

Long-term follow-up has further reinforced the durability of benefit. Extended analyses demonstrated a median overall survival exceeding four years, durable complete responses, and prolonged treatment-free survival in a subset of patients. Updated analyses continue to support nivolumab plus ipilimumab as a preferred first-line treatment for IMDC intermediate- and poor-risk disease (32).

The ability of dual checkpoint blockade to induce durable responses and potential long-term disease control distinguishes it from earlier targeted therapies and represents one of the most important advances in RCC therapeutics.

ICI–TKI Combination Therapy

Recognition of the immunomodulatory effects of VEGF inhibition provided the rationale for combining immune checkpoint inhibitors with VEGF-targeted therapies. VEGF promotes immune suppression by impairing dendritic-cell

maturation, reducing T-cell infiltration, and increasing regulatory T-cell populations. VEGF inhibition therefore creates a more favorable tumor microenvironment for immune activation (23-25).

Several phase III trials evaluating ICI–TKI combinations have demonstrated remarkable improvements in survival and response rates, leading to their widespread adoption as first-line treatment options.

Keynote-426
The phase III KEYNOTE-426 trial compared pembrolizumab plus axitinib with sunitinib in previously untreated advanced RCC (33).

The combination significantly improved overall survival, progression-free survival, and objective response rates. Initial analyses demonstrated a 47% reduction in the risk of death compared with sunitinib. Objective response rates exceeded 59%, establishing pembrolizumab plus axitinib as a highly effective first-line option applicable across all IMDC risk groups (33).

Javelin Renal 101
JAVELIN Renal 101 evaluated avelumab plus axitinib versus sunitinib in treatment-naïve advanced RCC (34).
The combination significantly improved progression-free survival and objective response rates. Although overall survival advantages were less pronounced than those observed with some other ICI-based combinations, the study confirmed the effectiveness of combining VEGF inhibition with immune checkpoint blockade and broadened available treatment options (34).

Checkmate 9ER
The phase III CheckMate 9ER trial evaluated nivolumab plus cabozantinib versus sunitinib as first-line therapy for advanced RCC (35).

The combination significantly improved progression-free survival (16.6 vs. 8.3 months), objective response rate (55.7% vs. 27.1%), and overall survival. Additionally, improved quality-of-life outcomes were observed compared with sunitinib. These findings established nivolumab plus cabozantinib as a highly effective treatment option across risk categories (35).

Clear Trial
The CLEAR trial compared pembrolizumab plus lenvatinib, lenvatinib plus everolimus, and sunitinib in treatment-naïve advanced RCC (36).
Pembrolizumab plus lenvatinib achieved one of the highest objective response rates reported in metastatic RCC, reaching approximately 71%. Median progression-free survival was 23.9 months, significantly longer than with sunitinib. Overall survival was also significantly improved, leading to widespread adoption of this regimen as a preferred first-line treatment option (36).

Cosmic-313
Despite significant advances with dual-agent combinations, outcomes remain suboptimal for many patients with aggressive disease. The phase III COSMIC-313 trial evaluated triplet therapy with nivolumab, ipilimumab, and cabozantinib compared with nivolumab plus ipilimumab alone in patients with intermediate- and poor-risk metastatic RCC (37).

The addition of cabozantinib significantly improved progression-free survival; however, toxicity increased substantially. Mature overall survival data remain under evaluation, and the precise role of triplet therapy in routine clinical practice continues to evolve (37).

Current Treatment Landscape
Immune checkpoint inhibitor-based combinations now represent the standard of care for most patients with newly diagnosed metastatic RCC. Selection among available regimens is guided by IMDC risk classification, disease burden, patient comorbidities, anticipated toxicities, and treatment goals. Dual checkpoint blockade offers the potential for durable treatment-free survival, whereas ICI–TKI combinations generally provide higher response rates and more rapid disease control.

Adjuvant Immunotherapy In RCC
The success of immune checkpoint inhibitors in metastatic RCC prompted investigation of their role in the adjuvant setting. Following nephrectomy, a substantial proportion of patients with high-risk localized RCC develop disease recurrence because of occult micrometastatic disease. Adjuvant immunotherapy aims to eradicate residual microscopic tumor deposits and improve long-term disease-free and overall survival (38-46).

Historically, VEGF-targeted therapies such as sunitinib, sorafenib, pazopanib, and axitinib were evaluated in the adjuvant setting. Although some studies demonstrated modest improvements in disease-free survival, toxicity was considerable and overall survival benefits remained uncertain, limiting routine clinical use (38-41).

Table 1: Landmark Immunotherapy Trials in Advanced RCC

Trial Name (Ref)	Combination Studied	Comparator Arm	Primary End Point	Sample Size	PFS, Median (months)	OS, Median (months)
CheckMate-214 (31,32)	Nivolumab + Ipilimumab	Sunitinib	OS, ORR	1096	11.6 vs 8.3 (HR 0.73)	NR vs 26.6 (HR 0.68)
KEYNOTE-426 (33)	Pembrolizumab + Axitinib	Sunitinib	OS, PFS	861	15.1 vs 11.1 (HR 0.69)	HR 0.53
JAVELIN Renal 101 (34)	Avelumab + Axitinib	Sunitinib	PFS	886	13.8 vs 8.4 (HR 0.69)	HR 0.80
CheckMate-9ER (35)	Nivolumab + Cabozantinib	Sunitinib	PFS, OS	651	16.6 vs 8.3 (HR 0.51)	HR 0.60
CLEAR (36)	Pembrolizumab + Lenvatinib	Sunitinib	PFS, OS	1069	23.9 vs 9.2 (HR 0.39)	HR 0.66
COSMIC-313 (37)	Nivolumab + Ipilimumab + Cabozantinib	Nivolumab + Ipilimumab	PFS	855	HR 0.73	OS immature

Keynote-564
KEYNOTE-564 represents the first positive phase III adjuvant immunotherapy trial in RCC and has fundamentally altered postoperative management of high-risk disease (42).

This multicenter randomized trial enrolled patients with clear-cell RCC at intermediate-high risk, high risk, or M1 no evidence of disease (M1-NED) following nephrectomy. Patients received pembrolizumab or placebo for one year.

Initial analyses demonstrated a significant improvement in disease-free survival, leading to regulatory approval of adjuvant pembrolizumab. Subsequent overall survival analyses confirmed a significant survival benefit, establishing pembrolizumab as the first adjuvant systemic therapy to demonstrate both disease-free and overall survival advantages in RCC (42,43).

The greatest benefit was observed in patients with high-risk pathological features and those rendered disease-free following metastasectomy. These findings support the concept that immunotherapy may be particularly effective against minimal residual disease.

IMmotion010
The phase III IMmotion010 trial evaluated adjuvant atezolizumab following nephrectomy in patients with RCC at increased risk of recurrence (44).

Despite encouraging results observed in metastatic disease, atezolizumab failed to demonstrate a significant improvement in disease-free survival compared with placebo. The study highlighted the complexity of translating successful metastatic immunotherapy strategies into the adjuvant setting and underscored the importance of patient selection and tumor biology (44).

CheckMate 914
CheckMate 914 evaluated adjuvant nivolumab plus ipilimumab following nephrectomy for localized RCC at high risk of recurrence (45).

Despite the proven efficacy of dual checkpoint blockade in metastatic disease, the trial failed to meet its primary endpoint of disease-free survival. Furthermore, toxicity was higher in the combination arm, resulting in increased treatment discontinuation rates. These findings suggest that the biological requirements for successful adjuvant therapy may differ substantially from those in advanced disease (45).

Prosper RCC
The PROSPER RCC trial explored a perioperative immunotherapy strategy involving neoadjuvant and adjuvant nivolumab (46).

Patients received nivolumab before surgery followed by postoperative treatment. However, the study did not demonstrate a significant recurrence-free survival benefit and was terminated early because of futility. The negative findings further emphasize the challenges associated with perioperative immunotherapy in RCC (46).

Current Role of Adjuvant Immunotherapy
At present, pembrolizumab remains the only immune checkpoint inhibitor with level I evidence supporting routine adjuvant use in RCC. Ongoing research seeks to identify biomarkers capable of predicting recurrence risk and immunotherapy responsiveness, thereby improving patient selection and minimizing overtreatment (42-46).

HIF-2α Inhibition: A New Therapeutic Paradigm
Although immune checkpoint inhibitors have transformed clinical outcomes, they do not directly target the fundamental molecular abnormalities driving clear-cell RCC. Advances in understanding RCC biology have identified hypoxia-inducible factor-2 alpha (HIF-2α) as a critical oncogenic driver and an attractive therapeutic target (47-49).

VHL–HIF Pathway
The hallmark molecular alteration in clear-cell RCC is loss or inactivation of the VHL tumor suppressor gene. Under normal oxygen conditions, VHL promotes degradation of HIF proteins. Loss of VHL function results in stabilization and accumulation of HIF-1α and HIF-2α, leading to activation of genes involved in angiogenesis, proliferation, metabolism, invasion, and metastasis (47).

Among these factors, HIF-2α appears to play a dominant oncogenic role. Increased HIF-2α activity stimulates expression of VEGF, PDGF, TGF-α, CXCR4, and cyclin D1, thereby promoting tumor progression and resistance to therapy (47-49).

Belzutifan
Belzutifan is a first-in-class selective HIF-2α inhibitor that directly targets the molecular driver of clear-cell RCC. Unlike VEGF inhibitors, which act downstream of HIF signaling, belzutifan inhibits transcriptional activity at its source, providing a novel mechanism of action (50).

Early clinical studies demonstrated durable antitumor activity with a favorable safety profile. The most common adverse events included anemia, fatigue, and hypoxia, reflecting the physiological role of HIF signaling in erythropoiesis and oxygen sensing (50).

Table 2: Major Adjuvant Immunotherapy Trials in RCC

Trial Name (Ref)	Intervention	Comparator	Population	Primary End Point	Sample Size	Result
ASSURE (38)	Sunitinib/Sorafenib	Placebo	High-risk RCC	DFS	1943	Negative
S-TRAC (39)	Sunitinib	Placebo	High-risk ccRCC	DFS	615	Positive DFS benefit
PROTECT (40)	Pazopanib	Placebo	High-risk RCC	DFS	1538	Negative
ATLAS (41)	Axitinib	Placebo	High-risk RCC	DFS	724	Negative

KEYNOTE-564 (42,43)	Pembrolizumab	Placebo	Intermediate-high/high-risk ccRCC, M1 NED	DFS/OS	994	Positive DFS and OS benefit
IMmotion010 (44)	Atezolizumab	Placebo	High-risk RCC	DFS	778	Negative
CheckMate-914 (45)	Nivolumab + Ipilimumab	Placebo	High-risk RCC	DFS	816	Negative
PROSPER RCC (46)	Perioperative Nivolumab	Observation	Resectable RCC	RFS	805	Negative

LITESPARK Clinical Development Program

The LITESPARK program has established belzutifan as one of the most promising recent advances in RCC therapeutics. LITESPARK-005 compared belzutifan with everolimus in previously treated advanced clear-cell RCC. The study demonstrated superior progression-free survival and objective response rates with belzutifan, supporting its role after progression on immunotherapy and VEGF-targeted therapy (51).

Additional studies have explored belzutifan in von Hippel–Lindau disease-associated RCC and combination regimens involving VEGF-targeted therapies and immune checkpoint inhibitors (52-55).

Future directions include evaluation of belzutifan in earlier disease settings, adjuvant therapy, and combination strategies designed to overcome resistance mechanisms and enhance treatment efficacy.

The emergence of adjuvant pembrolizumab and HIF-2α inhibition has expanded the therapeutic landscape of RCC beyond traditional metastatic disease management. While pembrolizumab currently remains the only approved adjuvant immunotherapy, belzutifan represents the first successful strategy targeting the central molecular driver of clear-cell RCC. Together, these advances are reshaping treatment paradigms and creating new opportunities for personalized management of RCC.

Table 3: Major HIF-2α Inhibitor Studies in RCC

Trial	Phase	Population	Intervention	Comparator	Primary End Point	Key Findings / Status	Ref
LITESPARK-001	Phase I	Advanced solid tumors / advanced ccRCC	Belzutifan monotherapy	None	Safety, ORR	First-in-human study. Demonstrated durable antitumor activity with acceptable safety after >41 months follow-up	(50)
LITESPARK-004	Phase II	VHL disease–associated RCC	Belzutifan monotherapy	None	ORR	Significant tumor regression and durable responses; formed basis for FDA approval in VHL-associated RCC	(52)
LITESPARK-005	Phase III	Previously treated advanced ccRCC after PD-(L)1 and VEGF-TKI therapy	Belzutifan	Everolimus	PFS	Improved PFS and ORR versus everolimus; established belzutifan as a treatment option in refractory RCC	(51)
LITESPARK-003	Phase II	Advanced ccRCC	Belzutifan + Cabozantinib	None	ORR, PFS	Demonstrated promising antitumor activity and response rates in treatment-naïve disease	(54)
LITESPARK-011	Phase III	Advanced RCC after prior anti–PD-(L)1 therapy	Belzutifan + Lenvatinib	Cabozantinib	PFS	Positive phase III study; significant improvement in PFS and ORR reported	(55)
LITESPARK-012	Phase III	First-line advanced ccRCC	Belzutifan-containing combinations (Pembrolizumab/Lenvatinib-based regimens)	Standard combination therapy	PFS	Ongoing/updated phase III trial evaluating incorporation of belzutifan into frontline therapy	(53)
LITESPARK-022	Phase III	High-risk localized ccRCC after nephrectomy	Pembrolizumab + Belzutifan	Pembrolizumab + Placebo	DFS	Adjuvant study; DFS benefit reported with ongoing OS evaluation	(56)
LITESPARK-033	Phase III	Recurrent RCC after prior adjuvant PD-1/PD-L1 therapy	Belzutifan + Zanzalintinib	Cabozantinib	PFS	Ongoing study addressing post-adjuvant immunotherapy recurrence.	(57)

Biomarkers of Response to Immunotherapy

The expanding therapeutic landscape of RCC has increased interest in identifying predictive biomarkers capable of guiding treatment selection and improving outcomes.

PD-L1 Expression

PD-L1 expression is associated with aggressive tumor biology and poor prognosis; however, its predictive value remains inconsistent. Responses to immune checkpoint inhibitors occur regardless of PD-L1 status, limiting its utility as a stand-alone biomarker in clinical practice (58).

PBRM1 Mutations

PBRM1 is one of the most frequently mutated genes in clear-cell RCC. Several studies suggest that PBRM1 loss may enhance responsiveness to immune checkpoint inhibition, although prospective validation remains necessary before routine clinical implementation (60).

Gene Expression Signatures
Transcriptomic analyses have identified angiogenic and immune-related signatures associated with treatment response. Angiogenic signatures may predict benefit from VEGF-targeted therapies, whereas T-effector and interferon-gamma signatures appear associated with responsiveness to immunotherapy (59,61,62).

Liquid Biopsy and Multi-Omics Approaches
Emerging technologies including circulating tumor DNA analysis, spatial transcriptomics, single-cell sequencing, and multi-omics profiling offer opportunities for more precise patient stratification and treatment selection. These approaches may play a central role in future precision oncology strategies (63,65).

Mechanisms of Resistance
Despite significant therapeutic advances, resistance to immunotherapy remains a major challenge, encompassing primary, adaptive, and acquired resistance mechanisms (65). Resistance may be classified as primary resistance, where tumors fail to respond initially, or acquired resistance, where disease progresses following an initial response, prompting the need for novel immunotherapies beyond conventional immune-checkpoint inhibition (66). Multiple mechanisms contribute to resistance, including:

- T-cell exhaustion mediated by persistent expression of inhibitory receptors such as PD-1, LAG-3, TIM-3, and TIGIT.
- VEGF-mediated immunosuppression leading to impaired immune-cell infiltration and antigen presentation (67).
- Expansion of regulatory T cells and myeloid-derived suppressor cells (69).
- Metabolic alterations within the tumor microenvironment.
- Defective antigen presentation and tumor antigen loss.

Understanding these mechanisms is critical for the development of next-generation therapeutic strategies capable of overcoming resistance and extending durable responses (63-64).

Emerging Immunotherapeutic Strategies in RCC
Despite remarkable advances achieved with immune checkpoint inhibitors and VEGF-targeted combinations, a substantial proportion of patients either fail to respond or eventually develop resistance. Consequently, considerable research efforts are focused on identifying novel immunotherapeutic approaches capable of enhancing response rates, overcoming resistance, and improving long-term disease control.

Novel Immune Checkpoints
Although PD-1, PD-L1, and CTLA-4 remain the principal therapeutic targets in RCC, emerging evidence suggests that additional inhibitory receptors contribute significantly to T-cell dysfunction and immune escape.

Lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) are increasingly recognized as important mediators of T-cell exhaustion within the RCC tumor microenvironment. These molecules are frequently co-expressed with PD-1 on dysfunctional CD8+ T cells and represent promising therapeutic targets for overcoming resistance to current immunotherapies (69-72). Early clinical studies evaluating LAG-3 and TIGIT inhibitors in combination with PD-1 blockade have demonstrated encouraging activity and may represent the next generation of checkpoint inhibition strategies.

Cytokine Engineering
While traditional cytokine therapies such as interferon-alpha and high-dose interleukin-2 were limited by significant toxicity, advances in protein engineering have led to the development of novel cytokine-based therapies with improved therapeutic indices.

Bempegaldesleukin (NKTR-214), a modified IL-2 agonist, was designed to preferentially stimulate CD8+ T cells and natural killer cells while minimizing activation of regulatory T cells. Although development has been challenging, cytokine engineering remains an active area of research (73).

Similarly, NHS-IL12 (M9241) delivers IL-12 directly to the tumor microenvironment, enhancing local immune activation while reducing systemic toxicity. Such approaches may eventually complement checkpoint blockade and improve antitumor immunity (74).

Bispecific Antibodies
Bispecific antibodies simultaneously bind tumor-associated antigens and immune effector cells, facilitating targeted immune-mediated tumor destruction.

XmAb819 is a bispecific antibody targeting ENPP3 on RCC cells and CD3 on T lymphocytes. Early-phase studies have demonstrated promising antitumor activity in heavily pretreated patients, supporting continued clinical development (75).

Unlike personalized cellular therapies, bispecific antibodies can be produced as off-the-shelf agents, potentially facilitating wider clinical implementation.

CAR-T and TCR-T Cell Therapies
Adoptive cellular therapies have transformed the treatment of hematological malignancies and are increasingly being explored in solid tumors, including RCC.

Chimeric antigen receptor T-cell (CAR-T) therapies target cell-surface antigens independently of major histocompatibility complex presentation, whereas T-cell receptor-engineered (TCR-T) therapies recognize intracellular tumor antigens presented through specific HLA molecules (76,77).

ALLO-316, a CD70-targeted allogeneic CAR-T therapy, has demonstrated encouraging activity in advanced RCC. Similarly, TCR-engineered therapies directed against HERV-E, a tumor-associated antigen selectively expressed in RCC, have shown early evidence of antitumor activity (76,77).

Although significant challenges remain, including tumor heterogeneity, trafficking barriers, and immunosuppressive

microenvironments, cellular therapies represent one of the most exciting future directions in RCC treatment.

Cancer Vaccines

Therapeutic cancer vaccines seek to stimulate tumor-specific immune responses through presentation of tumor-associated antigens.

IMA901, a multipeptide vaccine, and Rocapuldencel-T, a dendritic-cell-based vaccine, demonstrated immunogenicity but failed to produce significant improvements in clinical outcomes in randomized trials (78,79).

More recently, personalized mRNA vaccines have generated substantial interest following success in other malignancies. These vaccines can be tailored to individual tumor neoantigens and may synergize with checkpoint inhibition to enhance antitumor immunity (80).

Immunometabolic Targets

Metabolic dysregulation within the tumor microenvironment contributes significantly to immune resistance.

The adenosine pathway, mediated through CD39, CD73, and A2A receptors, suppresses T-cell function and promotes immune escape. Ciforadenant, an A2A receptor antagonist, has demonstrated encouraging activity in early clinical studies and represents a promising strategy for reversing adenosine-mediated immunosuppression (81).

Similarly, the indoleamine 2,3-dioxygenase (IDO) pathway contributes to immune evasion through tryptophan depletion and accumulation of immunosuppressive metabolites. Although early studies with epacadostat generated enthusiasm, subsequent trials yielded disappointing results. Nevertheless, the pathway remains under active investigation (82).

2. Future Directions

The future of RCC treatment will likely depend on improved biomarker-driven patient selection, rational combination therapies, and integration of novel therapeutic platforms. Continued advances in checkpoint biology, cellular therapies, HIF-2α inhibition, and precision oncology are expected to further improve outcomes and move the field closer to durable disease control and potential cure for a larger proportion of patients with advanced disease.

3. Conclusion

The treatment landscape of metastatic RCC has undergone a remarkable transformation over the past three decades. Progression from cytokine-based therapy to VEGF-targeted agents, immune checkpoint inhibitors, and HIF-2α inhibitors has substantially improved survival outcomes and quality of life. Immune checkpoint inhibitor-based combinations now represent the cornerstone of first-line treatment, while belzutifan has introduced a novel molecularly targeted approach directed against the fundamental biology of clear-cell RCC. Emerging strategies involving novel checkpoints, bispecific antibodies, cellular therapies, cancer vaccines, and precision biomarker-guided treatment hold significant promise. Continued advances in tumor immunology, molecular biology, and translational research are expected to further refine therapeutic approaches and improve long-term outcomes for patients with RCC

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