

Navigating the landscape of targeted therapies for renal cell carcinoma in the era of precision medicine (Review)

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Abstract. Renal cell carcinoma (RCC) is a biologically heterogeneous malignancy characterized by dysregulation of angiogenic signaling, immune evasion and epigenetic

remodeling. Advances in molecular profiling have redefined RCC as a pathway-driven disease, enabling the development of targeted therapies and immune checkpoint inhibitors (ICIs) that have notably improved clinical outcomes. The present review evaluated current evidence on the molecular basis and therapeutic landscape of RCC, with emphasis on von Hippel-Lindau-hypoxia-inducible factor signaling, chromatin remodeling alterations and immune regulatory pathways. The present review summarizes pivotal phase III clinical trials evaluating VEGF-targeted tyrosine kinase inhibitors, mechanistic target of rapamycin inhibitors, immune checkpoint inhibitors and combination regimens, including nivolumab plus ipilimumab, pembrolizumab + axitinib and lenvatinib + pembrolizumab. Emerging biomarkers, including International Metastatic Renal Cell Carcinoma Database Consortium risk stratification, programmed death-ligand 1 expression and chromatin remodeling gene alterations (polybromo 1/BRG1-associated factor 180, BRCA1-associated protein 1 and SET domain containing 2), are discussed in the context of their clinical utility and limitations. Despite marked progress, durable predictive biomarkers and optimal treatment sequencing strategies remain unresolved. Resistance to therapy emerges through adaptive angiogenic signaling, immune escape and metabolic reprogramming, underscoring the need for integrated multi-omics approaches and rational combination strategies. By integrating molecular biology with clinical trial evidence, the present review provides a structured framework for understanding therapeutic decision-making in RCC and highlights future directions toward biomarker-guided precision oncology.

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Abbreviations: RCC, renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; VHL, von Hippel-Lindau; HIF, hypoxia-inducible factor; EPAS1, endothelial PAS domain protein 1; PBRM1, polybromo 1/BRG1-associated factor 180; BAP1, BRCA1-associated protein 1; SETD2, SET domain containing 2; KDM5C, lysine-specific demethylase 5C; NF2, neurofibromatosis type 2; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; c-MET, cellular-mesenchymal-epithelial transition factor; FGFR, fibroblast growth factor receptor; GLUT1, glucose transporter 1; JAK, janus kinase; EMT, epithelial-mesenchymal transition; MDSC, myeloid-derived suppressor cell; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; HR, hazard ratio; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; NLR, neutrophil-to-lymphocyte ratio; LAG-3, lymphocyte-activation gene 3; TIGIT, T-cell immunoreceptor with Ig and ITIM domains

Key words: renal cell carcinoma, targeted therapies, precision medicine, immune checkpoint inhibitors, molecular mechanisms, biomarkers, clinical trials, tyrosine kinase inhibitors

Contents

1. Introduction
2. Genetic map of RCC
3. Molecular pathways in RCC
4. Current clinical research and evidence
5. Current directions and challenges
6. Conclusion

1. Introduction

Renal cell carcinoma (RCC) is a significant global health burden, accounting for 2-3% of all malignancies worldwide (1). According to GLOBOCAN 2024, kidney and renal pelvis cancer accounted for ~442,570 new cases and 144,871 mortalities worldwide in 2024, ranking 15th in incidence and 16th in mortality among all cancer types (2). Notably, there are marked geographical variations in incidence rates, with higher rates observed in North America and Europe compared with Asia and Africa. These differences may influence the prevalence of specific molecular subtypes and should be considered when designing region-specific treatment strategies. In the United States, RCC incidence has risen steadily over the past decades (3). Similarly, in Europe, incidence rates have increased, particularly among men. In East Asia, including China and Japan, RCC incidence remains relatively lower but is gradually rising, likely due to lifestyle changes and improved diagnostic techniques. These trends underscore the growing need for effective therapeutic strategies.

Despite advances in surgical techniques and systemic therapies, the prognosis for patients with advanced or metastatic RCC remains poor, with historical 5-year survival rates of <10% in the pre-targeted therapy era (3). Given the limitations of traditional cytokine-based therapies, the advent of targeted therapies and immune checkpoint inhibitors (ICIs) has notably changed the RCC treatment landscape. The majority of RCC cases are diagnosed at an early stage, but a notable proportion progress to advanced stages despite initial treatment. Current first-line systemic therapy for advanced clear cell renal cell carcinoma (ccRCC) is dominated by ICI-based combinations, including dual-ICI and ICI-tyrosine kinase inhibitor (TKI) regimens; VEGF-TKI monotherapy remains appropriate in selected patients, whereas mTOR inhibitors are generally reserved for later-line or specific clinical contexts (4-8). However, resistance to these therapies frequently develops, leading to disease progression. Furthermore, the heterogeneity of RCC tumors poses additional challenges, as genetic and molecular variations influence treatment response. There is an urgent need for novel therapeutic approaches, particularly those capable of overcoming resistance mechanisms and improving patient outcomes.

The landscape of cancer treatment has been transformed by targeted therapies that specifically inhibit molecular pathways implicated in carcinogenesis. In RCC, the therapeutic landscape has similarly evolved, with multiple targeted agents having established clinical roles across different treatment settings, including sunitinib, pazopanib, axitinib, cabozantinib, everolimus and temsirolimus (7,9-11). Despite these therapies having improved progression-free survival (PFS), their impact on overall survival (OS) remains variable, prompting ongoing research into novel targets and combination strategies.

The present review aimed to comprehensively evaluate the current state of targeted therapies for RCC in the precision oncology era. By synthesizing evidence from preclinical studies, primary-source clinical trials and contemporary clinical guidance, the present review offers clinicians and researchers a structured, evidence-based analysis of the evolving RCC therapeutic landscape. Furthermore, established and emerging approaches are examined, including an

assessment of controversies, failed strategies and unresolved questions.

2. Genetic map of RCC

RCC has a complex genetic landscape that notably influences its pathogenesis, progression and response to targeted therapy. Von Hippel-Lindau (VHL) inactivation is a key molecular event in ccRCC, while recurrent co-alterations in chromatin-remodeling genes such as polybromo 1/BRG1-associated factor 180 (PBRM1), BRCA1-associated protein 1 (BAP1) and SET domain containing 2 (SETD2) further shape tumor biology and therapeutic vulnerability across anti-angiogenic, immunotherapy and hypoxia-inducible factor (HIF)-targeted approaches. This genetic map informs precision medicine approaches. Table I summarizes the key genetic alterations in RCC and their clinical implications.

Genes regulating key signaling pathways

VHL gene. The VHL gene, located on chromosome 3p25-26, is a well-established tumor suppressor gene. VHL mutations are predominantly found in ccRCC, accounting for 60-80% of cases. It encodes a protein that has an important function in regulating HIFs, primarily HIF-1 α and HIF-2 α . Under normoxic conditions, VHL protein targets HIFs for ubiquitination and subsequent proteasomal degradation. When VHL function is lost due to mutations or deletions, HIFs accumulate and translocate to the nucleus, initiating transcription of numerous genes involved in angiogenesis, glucose metabolism, cell proliferation and survival (12).

VHL inactivation underpins the biological rationale for VEGF- and HIF-directed therapies in ccRCC. However, VHL status has not been prospectively validated as a predictive biomarker for selecting VEGF-targeted therapy and routine treatment selection based on VHL alteration status is not established (7,12).

While VHL/HIF pathway activation represents the central oncogenic driver in ccRCC, the clinical heterogeneity and variable treatment responses observed across patients cannot be fully explained by VHL status alone. Recent genomic studies have revealed that co-occurring alterations in chromatin remodeling genes, including PBRM1, BAP1 and SETD2, further modulate tumor biology and may create additional therapeutic vulnerabilities (13,14). Overall, the ccRCC genetic landscape is characterized by VHL inactivation as a key molecular event, with co-occurring alterations in chromatin remodeling (PBRM1, BAP1 and SETD2) and epigenetic regulators creating distinct therapeutic vulnerabilities that extend beyond the VEGF-HIF axis alone.

Endothelial PAS domain protein 1 (EPAS1; HIF-2 α). EPAS1 (encoding HIF-2 α) is a transcription factor involved in cellular hypoxia response. Under normoxic conditions, HIF-2 α is hydroxylated and targeted for proteasomal degradation by the VHL tumor suppressor protein (15). Under hypoxic conditions or in VHL-inactivated tumors, HIF-2 α dimerizes with HIF-1 β , translocates to the nucleus and binds hypoxia-response elements (HREs) on target genes (16). This activates transcription of genes involved in angiogenesis, glucose metabolism and cell survival, contributing to the aggressive RCC phenotype (12).

Table I. Key genetic alterations in renal cell carcinoma.

Gene	Chromosomal location	Function	Frequency/expression in ccRCC	Clinical importance	(Refs.)
VHL	3p25-26	Tumor suppressor; HIF regulation	60-80%	Biologically associated with HIF-VEGF axis activation; predictive value for anti-angiogenic therapy remains investigational	(12,50)
EPAS1 (HIF-2 α)	2p21	Transcription factor; hypoxia response	Frequently upregulated in VHL-deficient ccRCC	Therapeutic target (belzutifan); prognostic associations of HIF-2 α expression remain context-dependent and are not clinically validated	(15,16,19,20)
PBRM1	3p21.1	Chromatin remodeling (SWI/SNF complex)	30-40%	Association with ICI response remains controversial; variable prognostic impact	(23,24,26,27)
BAP1	3p21.1	Nuclear deubiquitinase; DNA repair	10-15%	Poor prognosis; aggressive tumor features; potential DNA repair-associated therapeutic vulnerability remains investigational	(31,33,35)
SETD2	3p21.31	Histone methyltransferase (H3K36me3)	~15%	Poor prognosis; potential therapeutic vulnerabilities in SETD2-deficient tumors; clinical predictive value unvalidated	(36-39)
KDM5C	Xp11.22	Histone demethylase (H3K4)	Recurrently mutated at relatively low frequency	Context-dependent epigenetic effects; clinical prognostic and predictive importance remains investigational	(40)
NF2	22q12	Tumor suppressor; Hippo pathway regulator	Infrequent but recurrently altered in RCC	Uncommon in ccRCC; associated with Hippo/YAP-TAZ pathway dysregulation; clinical prognostic importance remains unvalidated	(42,43)
PTEN	10q23.31	Phosphatase; PI3K/Akt negative regulator	5-10%	Poor prognosis; preclinical therapeutic vulnerability to PI3K/Akt/mTOR inhibition; clinical predictive value remains unvalidated	(21)

ccRCC, clear cell renal cell carcinoma; VHL, von Hippel-Lindau; HIF, hypoxia-inducible factor; PBRM1, polybromo 1/BRG1-associated protein 1; SETD2, SET domain containing 2; KDM5C, lysine-specific demethylase 5C; NF2, neurofibromatosis type 2; ICI, immune checkpoint inhibitor; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ binding motif; EPAS1, endothelial PAS domain-containing protein 1; SWI/SNF, with/sucrose non-fermentable chromatin remodeling complex.

In ccRCC, which constitutes 70-80% of all RCC cases, HIF-2 α is frequently upregulated due to VHL mutations (12). This contributes to expression of downstream targets including VEGF, platelet-derived growth factor (PDGF) and glucose transporter 1 (GLUT1), supporting tumor growth and angiogenesis (16). Preclinical studies have shown that HIF-2 α inhibition can reduce tumor growth and vascularization in ccRCC models (16-18). Associations between HIF-2 α expression and clinicopathological prognosis have varied according to assay methodology and cellular localization. Accordingly, HIF-2 α is currently more well established as a therapeutic target rather than a validated prognostic biomarker in ccRCC. Belzutifan demonstrated proof-of-concept efficacy in VHL disease-associated RCC (19), while in sporadic ccRCC after prior systemic therapy, belzutifan showed PFS benefit vs. everolimus (20). These data support HIF-2 α as a therapeutic target, though patient populations and evidence levels differ.

PTEN and PI3K/Akt regulation. The PTEN gene, located at 10q23.31, encodes a phosphatase that negatively regulates the PI3K/Akt signaling pathway by dephosphorylating PIP3 (21). PTEN mutations or deletions in ccRCC are associated with constitutive PI3K/Akt activation, which may promote cell proliferation, survival and resistance to apoptosis (21). PTEN alterations are associated with aggressive tumor features, poor prognosis, shorter OS and increased metastasis risk (21). Preclinical studies have suggested PTEN-deficient tumors may be more susceptible to PI3K/Akt/mTOR inhibitors (21,22) (Fig. 1).

Genes involved in chromatin and epigenetic regulation

Molecular basis of PBRM1. The PBRM1 gene, located at 3p21.1, encodes BRG1-associated factor 180, a key component of the switch/sucrose non-fermentable chromatin remodeling complex. This complex regulates gene expression by altering chromatin structure, thereby influencing DNA transcription, replication and repair (23-25). In RCC, particularly ccRCC, PBRM1 is frequently mutated or inactivated, leading to impaired chromatin remodeling and aberrant gene expression (26). Loss of PBRM1 is associated with dysregulation of downstream targets including genes involved in cell proliferation (such as cyclin D1), angiogenesis (such as VEGFA) and metabolic pathways (such as solute carrier family 2, which encodes GLUT1).

PBRM1 mutations are identified in 30-40% of ccRCC cases, predominantly as inactivating mutations (26). Functionally, PBRM1 loss is associated with increased expression of HIF target genes (such as VEGFA and GLUT1), contributing to angiogenesis and glycolysis (26). PBRM1-deficient cells demonstrate enhanced migratory and invasive capabilities, suggesting a role in metastatic progression (26,27). Clinically, PBRM1-mutant tumors are associated with more advanced disease stages and variable PFS outcomes (27). The association between PBRM1 alterations and immunotherapy response remains an active area of investigation with conflicting data. Liu *et al* (28) reported that PBRM1 loss was associated with reduced immune infiltration and potential resistance to checkpoint inhibitors in the IMmotion150 and Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets cohorts. Conversely, Miao *et al* (29) reported that PBRM1 loss-of-function was associated

with clinical benefit from programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade in ccRCC and Braun *et al* (30) further supported this association in an independent randomized-trial cohort, potentially through modulation of the tumor immune microenvironment. These discordant findings likely reflect differences in patient populations, co-occurring mutations (particularly BAP1 status) and the specific immunotherapy regimens evaluated. Prospective biomarker-embedded trials are needed to resolve this controversy. Integrated genomic analyses reveal that PBRM1 mutations frequently co-occur with VHL inactivation and SETD2 mutations, indicating complex genetic interplay in ccRCC development (23,24,26,27).

Clinical relevance of BAP1. The BAP1 gene, located at 3p21.1, encodes a nuclear deubiquitinase involved in gene expression regulation, DNA repair, cell cycle progression and apoptosis (31,32). BAP1 interacts with BRCA1 and other proteins to maintain genomic stability by removing ubiquitin modifications from histones and proteins, thereby modulating chromatin structure (31).

BAP1 dysfunction in ccRCC is associated with tumor development through increased genomic instability, chromatin remodeling defects and impaired DNA damage response (31,33). In genetically engineered mouse models, BAP1 loss has been shown to drive ccRCC development and is associated with high-grade tumor phenotypes and mTORC1 activation (34). Clinically, BAP1 mutations and protein loss have been associated with aggressive tumor features including high Fuhrman grade, advanced stage and poor prognosis (33,35). Patients with BAP1-altered tumors exhibit shorter OS and PFS compared with those with intact BAP1 (33,35). BAP1 loss disrupts DNA-damage responses and has provided a mechanistic rationale for exploring DNA-repair-directed strategies; however, whether BAP1 status predicts sensitivity to poly(ADP-ribose) polymerase inhibition or immune checkpoint blockade in RCC remains unproven (31,33).

Therapeutic targeting of SETD2. SETD2, located at 3p21.31, encodes the principal histone methyltransferase responsible for H3K36 trimethylation and contributes to transcriptional fidelity, DNA-damage responses and genomic stability. Loss of SETD2 in RCC leads to broad epigenetic and genomic dysregulation (36-38). Preclinical RCC models further suggest that SETD2 loss may create therapeutic vulnerabilities, including increased sensitivity to PI3K β /Akt inhibition, despite no SETD2-based predictive strategy having been clinically validated (39).

Lysine-specific demethylase 5C (KDM5C) and chromatin remodeling. The KDM5C gene, located at Xp11.22, encodes a histone lysine demethylase that specifically removes methyl groups from lysine 4 of histone H3, serving a key role in transcriptional regulation and chromatin remodeling. KDM5C contains numerous functional domains including a catalytic JmjC domain, zinc finger-C5HC2 domain, JmjN domain, Bright/ARID DNA-binding domain and two plant homeodomain fingers for histone binding (40). In ccRCC, KDM5C mutations are identified at relatively low frequency and are generally associated with loss of function and altered histone methylation patterns (40). Preclinical studies have suggested that KDM5C loss may produce context-dependent epigenetic

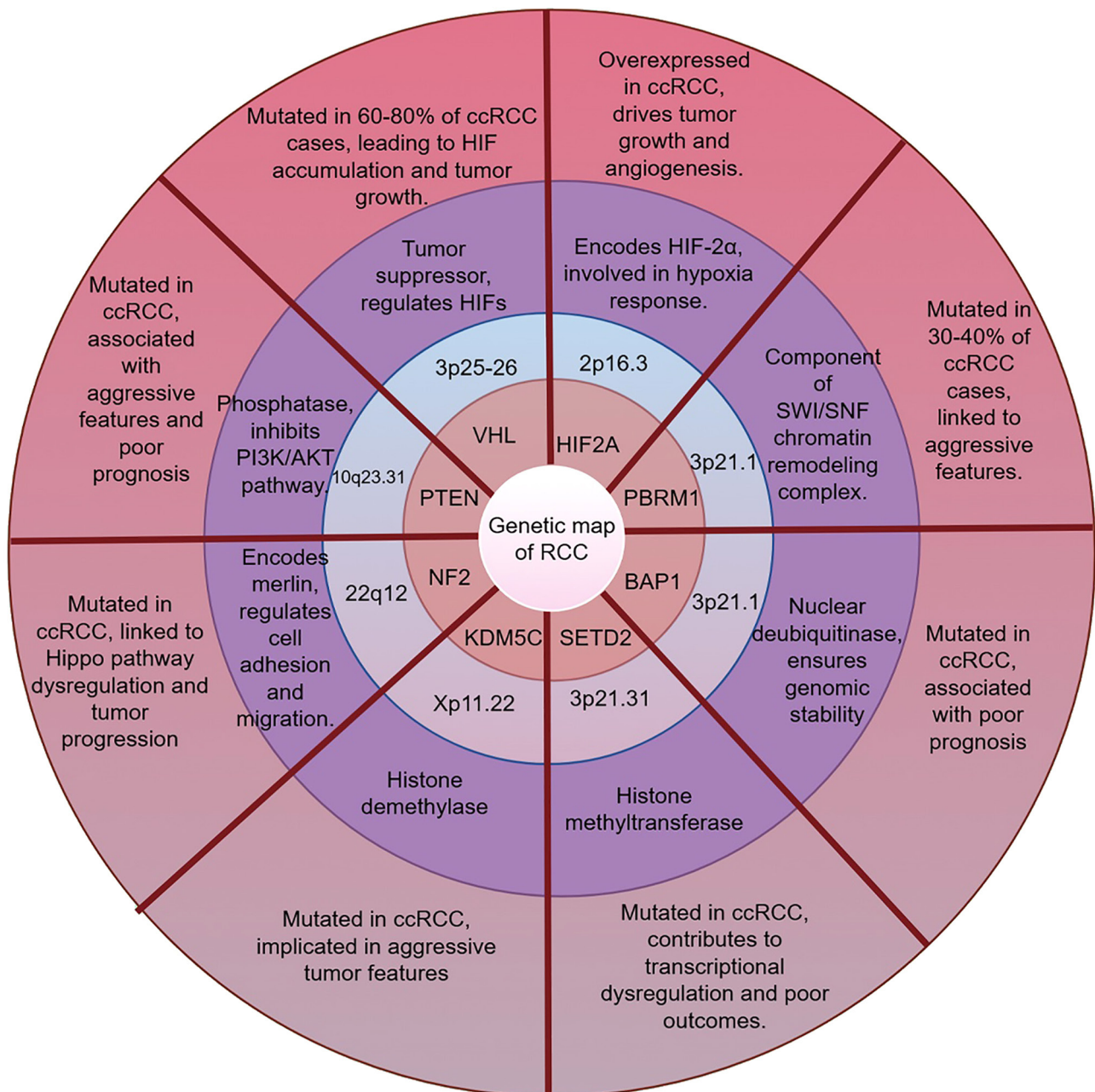


Figure 1. Genetic landscape of renal cell carcinoma. The associations between various genes and RCC are shown. The visualization integrates various genetic alterations such as histone modifiers and nuclear deubiquitinases, signifying their role in genomic stability and the regulation of gene expression, both of which have notable implications for developing targeted therapies. These alterations contribute to RCC pathogenesis and may influence prognosis, therapeutic vulnerability or treatment response, although the strength and clinical maturity of evidence vary among individual genes. Figure created with Figdraw (www.figdraw.com). RCC, renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; SWI/SNF, switch/sucrose non-fermentable; NF2, neurofibromatosis type 2; VHL, von Hippel-Lindau; PBRM1, polybromo 1; BAP1, BRCA1-associated protein 1; KDM5C, lysine-specific demethylase 5C.

effects and create therapeutic vulnerabilities in experimental models; however, its clinical prognostic and predictive importance remains investigational (40,41).

Genes regulating cell morphology and the Hippo pathway
Neurofibromatosis type 2 (NF2) and the Hippo pathway. The NF2 gene, located at 22q12, encodes the protein merlin, which regulates cell adhesion, migration and proliferation by interacting with cell membrane and cytoskeleton components (42). Merlin functions upstream of Hippo/yes-associated protein (YAP) signaling to restrain YAP/transcriptional coactivator

with PDZ-binding motif (TAZ) activity and also interacts with focal-adhesion signaling (42). NF2 alterations are uncommon in ccRCC; when present, NF2 loss disrupts merlin-mediated Hippo pathway control, resulting in enhanced YAP/TAZ activity, increased cell proliferation and invasiveness and resistance to apoptosis (42,43).

3. Molecular pathways in RCC

RCC involves a complex interplay of molecular pathways that drive tumor progression, metastasis and resistance to

Table II. Key molecular pathways in RCC.

Pathway	Key components	Role in RCC	Approved/investigational agents	(Refs.)
VEGF signaling	VEGF-A and VEGFR-1/2/3	Angiogenesis; tumor vascularization	Sunitinib, pazopanib, axitinib, cabozantinib and tivozanib	(7,44,45)
HIF signaling	HIF-1 α , HIF-2 α and VHL	Hypoxia adaptation; metabolic reprogramming	Belzutifan (HIF-2 α inhibitor)	(15,16,20,47)
mTOR signaling	mTORC1, mTORC2 and TSC1/2	Cell proliferation and metabolism	Everolimus and temsirolimus	(9,48,51)
PI3K/Akt	PI3K, Akt and PTEN	Cell survival, proliferation and metabolism	Investigational (PI3K inhibitors and Akt inhibitors)	(21)
Ras/MAPK	KRAS, BRAF, MEK and ERK	Cell proliferation and differentiation	Investigational (MEK inhibitors)	(54)
Immune checkpoint	PD-1, PD-L1 and CTLA-4	Immune evasion	Nivolumab, pembrolizumab, avelumab and ipilimumab	(4,5,56,57)
c-MET	HGF and c-MET	Cell migration, invasion and angiogenesis	Cabozantinib	(73)
Metabolism	GLUT1, HK2, LDHA and GLS	Warburg effect; biosynthesis	Investigational metabolism-directed approaches; no established standard RCC therapy	(44,55)

RCC, renal cell carcinoma; HIF, hypoxia-inducible factor; VHL, von Hippel-Lindau; TSC1/2, tuberous sclerosis complex 1/2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HGF, hepatocyte growth factor; c-MET, cellular-mesenchymal-epithelial transition; GLUT1, glucose transporter 1; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; GLS, glutaminase.

therapy. The RCC therapeutic landscape involves three biologically relevant axes: the VHL-HIF-angiogenesis axis, the immune checkpoint axis and the chromatin-remodeling axis, each with distinct clinical implications and evidence levels. Understanding these pathways informs the development of targeted therapies and may ultimately improve patient outcomes. Table II summarizes the key molecular pathways, their key components and therapeutic targets in RCC.

Angiogenesis-associated pathways

VEGF pathway. The VEGF pathway is involved in regulating angiogenesis in RCC. VEGF upregulation is frequently driven by VHL mutations, which prevent HIF degradation and contribute to constitutive VEGF transcription (12,44). VEGF-A, the most studied isoform, binds to VEGFR-1 and VEGFR-2 on endothelial cells, activating downstream PI3K/Akt and MAPK pathways that may promote endothelial cell proliferation, migration and survival (45). VEGF pathway-targeted TKIs have improved outcomes in ccRCC, but intrinsic and acquired resistance remain key limitations of VEGF-directed therapy (45). Multi-target TKIs (such as cabozantinib) and combination strategies pairing VEGF inhibition with ICIs represent approaches aimed at addressing the adaptive capacity of RCC (46).

HIF-1 signaling and hypoxia adaptation. The HIF-1 signaling pathway is involved in RCC pathogenesis. HIF-1 α accumulation drives transcription of angiogenic and metabolic

genes (44,47), with PI3K/Akt/mTOR crosstalk enhancing oncogenic signaling (48). Direct HIF-1 α targeting has not yet yielded an established therapeutic strategy in RCC, whereas HIF-2 α has proved more pharmacologically tractable; efforts have therefore concentrated on downstream VEGF targets and HIF-2 α (49,50).

Cell proliferation and metabolism-associated pathways

mTOR pathway. The mTOR pathway is involved in regulating cell proliferation and metabolism. In RCC, mTOR activation occurs through TSC1/2 mutations or upstream PI3K/Akt dysregulation, which may contribute to uncontrolled cell proliferation (21,48). Both everolimus and temsirolimus are rapamycin (sirolimus) analogues that act as allosteric inhibitors of mTORC1, thereby blocking downstream protein synthesis and proliferative signaling; everolimus is an orally administered agent, whereas temsirolimus is an intravenously administered ester prodrug of sirolimus that is converted to sirolimus *in vivo*. Everolimus demonstrated PFS benefit after prior VEGF-targeted therapy (9), whereas temsirolimus improved OS in previously untreated poor-risk metastatic RCC (51). In the modern ICI/TKI era, mTOR inhibition therefore occupies a more limited and context-dependent role.

Preclinical genetically engineered mouse models have implicated BAP1 loss in enhanced mTORC1 activation, although whether BAP1 status confers differential sensitivity to mTOR inhibitors remains unresolved (34,52). In addition,

VEGFR-TKIs and mTOR inhibitors may exert immunomodulatory effects (such as a reduction of regulatory T cells and myeloid-derived suppressor cells, enhanced dendritic-cell antigen presentation and modulation of effector T-cell function) within the RCC tumor microenvironment, although the clinical predictive relevance of these immune effects remains uncertain (53).

PI3K/Akt and cell survival signaling. The PI3K/Akt pathway is initiated by growth factor binding to receptor tyrosine kinases, activating PI3K to convert PIP2 to PIP3, which recruits and activates Akt (21). Akt phosphorylates downstream effectors including mTOR, GSK3 β and FOXO transcription factors, which may promote cell survival and proliferation. In ccRCC, PIK3CA mutations and PTEN loss-of-function mutations are associated with constitutive pathway activation (21). Although PI3K/Akt signaling remains biologically relevant and selective PI3K or Akt inhibitors continue to be investigated, neither class has established a clinically validated single-agent role in RCC. By contrast, the downstream mTOR inhibitors everolimus and temsirolimus have demonstrated efficacy in defined clinical settings, although their roles have become more limited in the contemporary ICI/TKI era (9,21,51).

Ras/MAPK and proliferation control. Despite canonical KRAS mutations being uncommon in ccRCC, MAPK pathway activation may occur through upstream receptor tyrosine kinase signaling and pathway crosstalk (54). The Ras pathway intersects with the VHL-HIF pathway, with hypoxia-induced HIFs enhancing Ras-mediated oncogenic signaling (47). MEK inhibitors such as trametinib have shown promise in preclinical models (54), though clinical application remains limited by pathway redundancy and compensatory mechanisms. To the best of our knowledge, no MEK inhibitor has demonstrated RCC-specific clinical activity sufficient to advance to phase III development, illustrating the challenge of targeting downstream signaling nodes in a pathway-driven tumor.

Metabolic reprogramming in RCC. RCC exhibits profound metabolic reprogramming, including enhanced glycolysis (Warburg effect), glutaminolysis and lipid synthesis, driven by VHL-HIF pathway activation (44,55). While these metabolic alterations are well characterized biologically, to the best of our knowledge, no metabolism-targeted therapy has established clinical efficacy or a standard therapeutic role in RCC and metabolic interventions remain investigational. The primary therapeutic relevance of metabolic reprogramming currently lies in its role as a resistance mechanism to VEGF-TKIs and ICIs, rather than as a direct drug target.

Immune regulation-associated pathways

Immune checkpoint regulation in RCC. The PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) axes represent important therapeutic targets in RCC (56). PD-1 is an inhibitory receptor expressed on T cells; its ligand PD-L1 is frequently upregulated on RCC tumor cells. PD-1/PD-L1 interaction contributes to immune evasion by inhibiting T-cell activation (56). PD-L1 expression has been explored as a candidate biomarker in RCC trials; however, its predictive utility has been inconsistent across regimens and is insufficient for stand-alone treatment selection (4,56,57). CTLA-4 inhibits T-cell activation at an earlier stage than PD-1; CTLA-4

blockade enhances T-cell activation and tumor infiltration (56). The phase III Nivolumab + Ipilimumab vs. Sunitinib Trial (CheckMate 214) demonstrated durable clinical benefit with dual CTLA-4/PD-1 blockade compared with sunitinib in advanced RCC (4).

ICIs including nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) block these interactions, reactivating antitumor immune responses (4,46). Combination approaches pairing ICIs with anti-angiogenic agents have demonstrated improved antitumor activity compared with VEGF-TKI monotherapy in phase III trials (5,57), challenging the assumption that immunotherapy benefit operates independently of VEGF signaling. However, to the best of our knowledge, no direct ICI vs. ICI + TKI head-to-head trials exist to conclusively establish comparative efficacy.

IL-6/JAK/STAT3 signaling in RCC. The IL-6/JAK/STAT3 axis is a well-characterized oncogenic and immunomodulatory pathway across cancers (58,59). In metastatic ccRCC, elevated circulating IL-6 has been associated with poorer clinical outcomes and reduced response to sunitinib (60). Accordingly, the IL-6/JAK/STAT3 pathway remains an investigational therapeutic axis rather than an established treatment target in RCC.

Signal transduction-associated pathways

NF- κ B and TGF- β pathways. Both NF- κ B and TGF- β signaling are involved in RCC inflammatory microenvironment remodeling and immune evasion (61,62). NF- κ B activation is associated with pro-survival and pro-inflammatory gene expression, while TGF- β is implicated in immunosuppression through regulatory T-cell and myeloid-derived suppressor cell (MDSC) recruitment (61,62). Despite direct inhibitors of NF- κ B and TGF- β signaling existing and having been evaluated in preclinical and early-phase clinical studies (63-65), to the best of our knowledge, no study has demonstrated single-agent clinical activity in RCC. The therapeutic relevance of these pathways in RCC lies primarily in their role as mediators of resistance and microenvironmental modulators. TGF- β inhibitors, for instance, are being explored primarily as combination partners to enhance ICI efficacy by reversing immunosuppression, rather than as standalone RCC therapies. Similarly, NF- κ B modulation remains investigational, with its clinical utility currently limited to combination contexts aimed at overcoming resistance to established therapies.

Cell adhesion and migration-associated pathways

Epithelial-mesenchymal transition (EMT) and metastatic potential. EMT contributes to RCC metastatic dissemination and therapy resistance through transcriptional reprogramming (15,44). However, EMT may represent a secondary consequence of oncogenic signaling (VHL-HIF, TGF- β and receptor tyrosine kinase activation) rather than a primary therapeutic target. No EMT-targeted agent has demonstrated RCC-specific clinical activity and the concept of EMT as a therapeutic target, despite extensive preclinical literature, lacks sufficient prospective validation in RCC. EMT remains a descriptive biological phenomenon rather than a druggable target, with its clinical relevance limited to association with aggressive disease phenotypes and as a potential biomarker of resistance to VEGF-TKIs and ICIs (66).

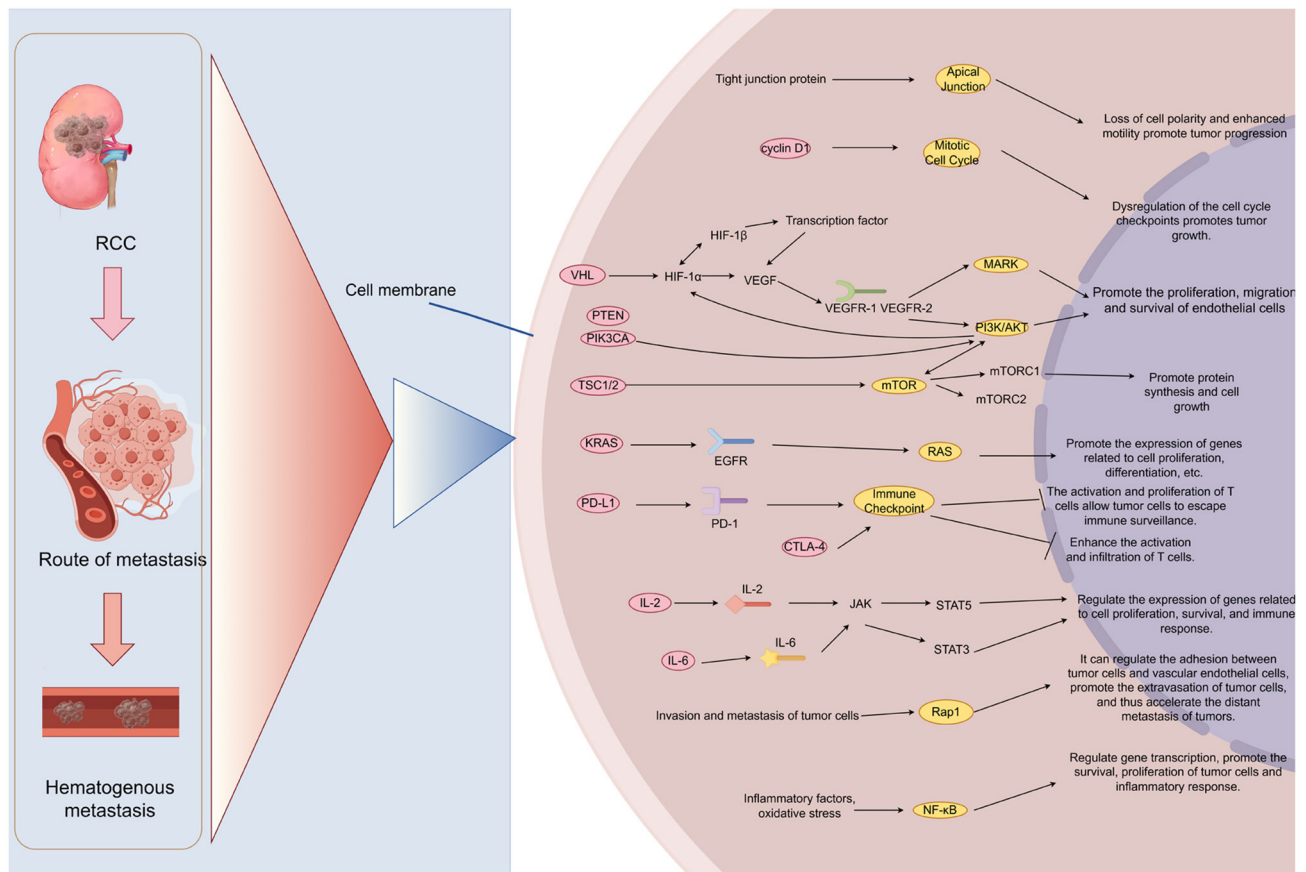


Figure 2. Key molecular pathways driving RCC progression and therapeutic targeting. Schematic diagram of the molecular mechanisms underlying the key targeted pathways in renal cell carcinoma. The figure presents a detailed schematic of the signaling pathways and mechanisms involved in the progression and metastasis of renal cell carcinoma, focusing on key targets for potential therapies. This pathway map highlights key molecular players and their interactions that drive tumorigenesis and metastatic spread, offering insights into potential therapeutic targets in the era of precision medicine. Figure created with Figdraw (www.figdraw.com). RCC, renal cell carcinoma; HIF, hypoxia-inducible factor; VHL, von Hippel-Lindau; KRAS, Kirsten rat sarcoma viral oncogene homolog; RAS, rat sarcoma virus; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Rap1, Ras-proximate-1.

Inflammatory response-associated pathways

Inflammatory response pathway. The inflammatory response pathway in RCC involves a number of cytokines, chemokines and immune cells. The IL-6 signaling axis is implicated in tumor growth, angiogenesis and immune evasion through JAK/STAT pathway activation (58,59). Tumor-associated macrophages adopt pro-tumorigenic phenotypes that support tumor growth and metastasis (61,62). Conceptually, inflammatory signaling bridges the angiogenic and immune axes in RCC, explaining why anti-inflammatory strategies alone have not achieved clinical utility while combination approaches targeting both inflammation and angiogenesis or immune checkpoints remain under active investigation.

Immune infiltration patterns differ significantly among RCC molecular subtypes and may influence the response to immunotherapy (67); however, no inflammation-based signature has yet been sufficiently prospectively validated for routine treatment selection. High systemic inflammation, as measured by neutrophil-to-lymphocyte ratio (NLR) or C-reactive protein, is associated with poor prognosis (68).

Other pathways

Cell cycle dysregulation in RCC. Cell cycle dysregulation in RCC involves frequent alterations in CDK signaling,

cyclin expression and checkpoint control, contributing to uncontrolled proliferation (67). Collectively, RCC molecular pathogenesis is driven by coordinated dysregulation across angiogenic, immune and epigenetic-metabolic axes rather than isolated pathway activation, suggesting that therapeutic strategies should address this multi-dimensional biology to achieve durable clinical benefit (Fig. 2).

4. Current clinical research and evidence

Targeted therapies have evolved notably in the pursuit of precision medicine for RCC, offering diverse therapeutic options. Phase III evidence establishes ICI combinations as active first-line approaches, though trial diversity and the absence of head-to-head comparisons limit definitive treatment hierarchies. The following sections discuss clinical research and evidence across various targeted approaches, from VEGF inhibition and mTOR-targeted therapies to immunotherapies and emerging combinations, highlighting advancements, comparative insights, challenges and the role of biomarkers in guiding treatment decisions. Efficacy data are primarily drawn from pivotal trial publications, supplemented by mature or final follow-up analyses where clinically relevant.

Targeted VEGF inhibition in RCC. The VEGF pathway is an important driver of angiogenesis and tumor growth in RCC. First-generation VEGF receptor TKIs established the foundation for targeted therapy. In a pivotal phase III trial, sunitinib demonstrated a median PFS of 11 months compared with 5 months with interferon- α and an objective response rate (ORR) of 31 vs. 6% (11,69). Sorafenib improved median PFS to 5.5 months compared with 2.8 months with placebo in the TARGET trial (70). Axitinib, a second-generation selective TKI, exhibited improved PFS (6.7 months) compared with sorafenib (4.7 months) in previously treated advanced RCC (71).

Combination therapies are being explored to address therapeutic resistance. A Phase Ib trial of axitinib + pembrolizumab reported a 58% ORR and a median PFS of 20.9 months in the dose-expansion cohort, illustrating the complementary mechanisms of VEGF inhibition and immune checkpoint blockade (72). Next-generation VEGF inhibitors such as cabozantinib target mesenchymal-epithelial transition (MET) and AXL in addition to VEGFR. The Cabozantinib vs. Everolimus in Advanced Renal-Cell Carcinoma Trial (METEOR) demonstrated that cabozantinib significantly improved PFS [7.4 vs. 3.9 months; hazard ratio (HR) 0.51; $P < 0.0001$] and OS (21.4 vs. 17.1 months; HR 0.70; $P = 0.0002$) compared with everolimus in previously treated patients (73,74). The Cabozantinib vs. Sunitinib in Metastatic Renal Cell Carcinoma Trial (CABOSUN) demonstrated that cabozantinib improved median PFS compared with sunitinib as first-line therapy in intermediate- and poor-risk patients (8.6 vs. 5.3 months by independent review; HR 0.48), with updated median OS of 26.6 vs. 21.2 months (HR 0.80) (75,76).

Tivozanib is a highly selective VEGFR-1/2/3 inhibitor with a narrower kinase inhibition profile compared with broader-spectrum TKIs. Its clinical activity was initially demonstrated in the phase III TIVO-1 trial (77), while the phase III TIVO-3 trial further supported its role in previously treated advanced RCC by showing improved PFS compared with sorafenib (78). Therefore, tivozanib is best discussed as a VEGFR-selective option with particular relevance in the later-line setting rather than as a broadly preferred first-line standard (77,78). Despite these advancements, challenges persist. Biomarkers to predict VEGF inhibitor response remain limited and angiogenesis pathway redundancy contributes to treatment failure (66). The broader toxicity profile of cabozantinib (including palmar-plantar erythrodysesthesia and gastrointestinal adverse events) requires experience in management (79) (Table III).

mTOR-targeted therapies. The mTOR pathway regulates cell proliferation and angiogenesis in RCC. The Renal Cell Cancer Treatment with Oral RAD001 Given Daily Trial (RECORD-1) trial established everolimus as a commonly used second-line therapy after TKI failure, demonstrating a median PFS of 4.9 vs. 1.9 months for placebo ($P < 0.001$) (9). Subsequent phase II studies further evaluated single-agent everolimus in metastatic RCC. The phase II trial by Amato *et al* (80) reported disease stabilization and prolonged progression-free survival in patients with predominantly ccRCC, supporting the antitumor activity of mTOR inhibition in this setting. Temsirolimus demonstrated superior survival benefits in patients with poor

prognosis. The Advanced Renal Cell Carcinoma Trial revealed a median OS of 10.9 months for temsirolimus vs. 7.3 months for interferon- α ($P = 0.008$) in untreated high-risk patients with metastatic RCC (51).

Biomarkers are key for personalizing mTOR-targeted therapy. Combined subgroup analyses of the RECORD-1 and REACT trials demonstrated that hyperglycemia and hypercholesterolemia during everolimus treatment associated with improved PFS (7.4 vs. 5.3 months, $P = 0.01$), suggesting metabolic toxicity as a potential surrogate for drug activity (81). Proactive management of everolimus-associated adverse events, including stomatitis, noninfectious pneumonitis and metabolic abnormalities, is important for maintaining dose intensity (82).

Targeting PD-1/PD-L1 and CTLA-4 in RCC. The PD-1/PD-L1 axis is key in tumor immune evasion. Nivolumab, a monoclonal antibody targeting PD-1, demonstrated notable efficacy in advanced RCC after prior VEGF-targeted therapy. In the phase III CheckMate 025 trial, nivolumab showed superior OS compared with everolimus (25.0 vs. 19.6 months; HR 0.73; $P = 0.002$) with an ORR of 25 vs. 5% (83).

Ipilimumab + nivolumab combination therapy has reshaped first-line treatment. In an 8-year analysis of CheckMate 214, nivolumab + ipilimumab maintained an OS benefit vs. sunitinib in both the intention-to-treat population (median OS, 52.7 vs. 37.8 months; HR 0.72, 95% CI 0.62-0.83) and the intermediate/poor-risk population (median OS, 46.7 vs. 26.0 months; HR 0.69, 95% CI 0.59-0.81) (84). In the intent-to-treat (ITT) population, median PFS was similar (12.4 vs. 12.3 months; HR 0.88), whereas greater PFS separation was observed in the intermediate/poor-risk subgroup. At the final analysis with 9.3 years of median follow-up, the OS benefit remained durable in the ITT population (HR 0.71; 95% CI 0.62-0.82), with estimated 108-month OS probabilities of 31.4 vs. 19.5% (85).

The Pembrolizumab + Axitinib vs. Sunitinib Trial (KEYNOTE-426) demonstrated efficacy over sunitinib in the first-line setting, with a median OS of 47.2 vs. 40.8 months (HR 0.84; 95% CI 0.71-0.99) and median PFS of 15.7 vs. 11.1 months (HR 0.69; 95% CI 0.59-0.81) (5). The ORR was 60.6 vs. 39.6%, with complete responses in 11.6 vs. 4.0% of patients. In addition, 5-year follow-up data demonstrated durable benefit (5).

The Avelumab + Axitinib vs. Sunitinib Trial (JAVELIN Renal 101) exhibited significant PFS improvement compared with sunitinib in the primary analysis (13.8 vs. 8.4 months; HR 0.69; 95% CI 0.574-0.825; $P < 0.0001$) (57). In the final analysis with a minimum follow-up of 68 months, median PFS was 13.9 vs. 8.5 months (HR 0.66) and the median OS was 44.8 vs. 38.9 months in the overall population (HR 0.88; 95% CI 0.749-1.039; $P = 0.0669$) and 43.2 vs. 36.2 months in the PD-L1-positive population (HR 0.86; 95% CI 0.701-1.057; $P = 0.0755$), favoring the avelumab + axitinib arm but not reaching statistical significance (86). The ORR was 59.7 vs. 32.0% (86). Nivolumab + cabozantinib also demonstrated durable first-line efficacy in CheckMate 9ER. In the final analysis (median follow-up, 5.6 years), median PFS was 16.4 vs. 8.3 months (HR 0.58) and median OS was 46.5 vs. 35.5 months (HR 0.79) compared with sunitinib (8).

Table III. Targeted therapeutic agents in RCC.

Target	Agent	Mechanism	Clinical indication	Key trial	(Ref.)
VEGFR-1/2/3	Sunitinib	Multi-targeted TKI	Selected/historical first-line option for advanced RCC	Phase III vs. IFN- α (PFS 11 vs. 5 months)	(11)
VEGFR-1/2/3	Pazopanib	Multi-targeted TKI	Selected/historical first-line option for advanced RCC	Phase III vs. sunitinib (non-inferior)	(95)
VEGFR-1/2/3 VEGFR, MET and AXL	Axitinib Cabozantinib	Selective VEGFR TKI Multi-targeted TKI	Second-line advanced RCC Later-line therapy; historical first-line evidence in intermediate/poor-risk disease	AXIS (PFS 6.7 vs. 4.7 months vs. sorafenib) METEOR and CABOSUN	(71) (73,75)
VEGFR-1/2/3	Tivozanib	Selective VEGFR TKI	Later-line advanced RCC after prior systemic therapy; earlier-line activity evaluated in TIVO-1	TIVO-3: PFS 5.6 vs. 3.9 months vs. sorafenib; TIVO-1: PFS benefit vs. sorafenib	(77,78)
mTORC1	Everolimus	mTOR inhibitor	Historical post-TKI/late-line option in selected patients	RECORD-1 (PFS 4.9 vs. 1.9 months)	(9)
mTORC1	Temsirolimus	mTOR inhibitor	Historical first-line evidence in untreated poor-risk RCC; limited contemporary role	ARCC (OS 10.9 vs. 7.3 months)	(51)
VEGFR, FGFR, PDGFR, RET and KIT	Lenvatinib	Multi-targeted TKI	First-line (combo); second-line (combo)	CLEAR and Study 205	(6,92)
HIF-2 α	Belzutifan	HIF-2 α inhibitor	Post-anti-PD-L1 and post-VEGF-TKI	LITESPARK-005	(20)

RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; MET, mesenchymal-epithelial transition; AXL, AXL receptor tyrosine kinase; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; HIF, hypoxia-inducible factor; PFS, progression-free survival; OS, overall survival; NCT, ClinicalTrials.gov identifier; RET, rearranged during transfection; KIT, KIT proto-oncogene; PD-L1, programmed death-ligand 1; AXIS, Axitinib vs. Sorafenib in Advanced Renal Cell Carcinoma Trial; METEOR, Cabozantinib vs. Everolimus in Advanced Renal-Cell Carcinoma Trial; CABOSUN, Cabozantinib vs. Sunitinib in Metastatic Renal Cell Carcinoma Trial; RECORD-1, Renal Cell Cancer Treatment with Oral RAD001 Given Daily Trial; ARCC, Advanced Renal Cell Carcinoma Trial; CLEAR, Lenvatinib + Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma Trial; LITESPARK-005, Belzutifan vs. Everolimus for Advanced Renal-Cell Carcinoma Trial.

The Lenvatinib + Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma Trial (CLEAR) demonstrated that lenvatinib + pembrolizumab is an active first-line option. In the final prespecified OS analysis, median OS was 53.7 months with lenvatinib + pembrolizumab vs. 54.3 months with sunitinib (HR 0.79; 95% CI 0.63-0.99), while median PFS remained markedly longer with the combination (23.9 vs. 9.2 months; HR 0.47), with an ORR of 71.3 vs. 36.7% (6,87). However, the toxicity profile of lenvatinib + pembrolizumab (including hypertension, diarrhea and proteinuria) requires careful patient selection and monitoring.

Targeting fibroblast growth factor receptor (FGFR), cellular (c)-MET and HIF-2 α . FGF/FGFR signaling has been implicated as a bypass pathway contributing to resistance to VEGF-directed therapy in RCC (66). However, FGFR-targeted agents have not established a validated clinical role in RCC and RCC-specific prospective evidence remains limited. c-MET signaling is dysregulated in RCC, particularly in the papillary subtype (88). Cabozantinib, a multi-kinase inhibitor targeting c-MET, VEGFR and AXL, demonstrated efficacy in the METEOR trial in previously treated patients (73). Belzutifan, a HIF-2 α inhibitor, demonstrated proof-of-concept efficacy in VHL disease-associated RCC (19) and in post-treatment sporadic ccRCC (20).

Combination therapy. Combination therapies integrating ICIs with TKIs or dual checkpoint blockade have emerged as clinically impactful approaches. Table IV presents verified efficacy data from pivotal phase II and III trials. Furthermore, the heterogeneity and complexity of RCC necessitate multifaceted treatment strategies. Combination therapies targeting distinct pathways can synergistically inhibit tumor growth and angiogenesis while mitigating resistance. Pairing ICIs with VEGF-TKIs leverages immune recognition complemented by anti-angiogenic effects, creating a more favorable tumor microenvironment.

The CheckMate 214 trial established nivolumab + ipilimumab as a commonly used option for intermediate- and poor-risk patients, demonstrating improved long-term OS and ORR compared with sunitinib (Table IV) (84). However, nivolumab + ipilimumab has a distinct immune-mediated toxicity profile. In long-term follow-up, overall grade 3-4 treatment-associated adverse events were less frequent compared with sunitinib, although immune-mediated adverse events may require corticosteroid treatment and can lead to treatment discontinuation (85,89). KEYNOTE-426, JAVELIN Renal 101 and CLEAR each demonstrated improved PFS for their respective ICI-TKI combinations compared with sunitinib (Table IV) (5,6,57).

A critical efficacy finding was demonstrated through the Belzutifan vs. Everolimus for Advanced Renal-Cell Carcinoma Trial (LITESPARK)-005, which evaluated belzutifan vs. everolimus in heavily pretreated patients (post-ICI and post-VEGF-TKI). While median PFS was identical between arms (5.6 vs. 5.6 months), PFS was significantly improved with belzutifan (HR 0.75, 95% CI 0.63-0.90; two-sided log-rank $P=0.002$) and ORR favored belzutifan (21.9 vs. 3.5%), OS did not reach statistical significance (HR 0.88; 95% CI 0.73-1.07; $P=0.200$), representing an important limitation in

this refractory population (20). The absence of a statistically significant OS advantage at the reported analysis tempers enthusiasm for belzutifan monotherapy in this population and combination strategies may further define its optimal clinical role. Other belzutifan-based combination strategies remain investigational, whereas LITESPARK-011 has now reported phase III efficacy results (90).

Building upon these findings, the phase III LITESPARK-011 trial (NCT04586231) evaluated belzutifan + lenvatinib vs. cabozantinib in patients with advanced clear cell RCC after progression on anti-PD-L1 therapy; at the second interim analysis, the combination significantly improved median PFS (14.8 vs. 10.7 months; HR 0.70; 95% CI 0.59-0.84; one-sided $P<0.0001$) and ORR (52.6 vs. 40.2%), while median OS (34.9 vs. 27.6 months; HR 0.85) did not reach statistical significance at the time of this interim analysis (90). In addition, the phase III LITESPARK-022 study (NCT05239728) evaluated adjuvant pembrolizumab + belzutifan vs. pembrolizumab plus placebo in patients with clear cell RCC at increased risk of recurrence after nephrectomy, demonstrating significantly improved disease-free survival (HR 0.72; 95% CI 0.59-0.87; two-sided $P<0.001$), although OS data remain immature (91). These trials support an expanding role for HIF-2 α -directed therapy across sequential, combination and adjuvant settings, although optimal patient selection, treatment sequencing and mature OS benefit remain to be defined.

The combination of lenvatinib + everolimus (Lenvatinib + Everolimus Combination Trial (Study 205)), a phase II three-arm trial in previously treated patients, demonstrated a median PFS of 14.6 vs. 5.5 months (HR 0.40; $P=0.0005$) and median OS of 25.5 vs. 15.4 months (HR 0.51; $P=0.024$) compared with everolimus alone (92). This supported subsequent first-line combination development.

Ongoing trials are exploring novel combinations, including the addition of C-X-C chemokine receptor type 4 (CXCR4) inhibitors to immunotherapy regimens. A phase Ib trial of the CXCR4 inhibitor mavoxixafor in combination with nivolumab in patients with advanced ccRCC unresponsive to nivolumab monotherapy demonstrated potential antitumor activity and a manageable safety profile (93). In addition, the search for reliable biomarkers to guide treatment selection and predict responses remains a key area of investigation.

5. Current directions and challenges

Precision therapy approaches in advanced RCC. The transition from empiric to precision therapy in RCC requires integrating molecular profiling, validated biomarkers and resistance-aware treatment sequencing, objectives that remain incompletely realized. Precision medicine in RCC has progressed beyond single-biomarker approaches toward integrated, multi-dimensional decision models. Molecular profiling at baseline establishes the biological rationale for subsequent therapeutic decisions. VHL mutation status represents a central biological axis: VHL inactivation activates the HIF-VEGF axis and provides a strong biological rationale for sensitivity to anti-angiogenic therapy (50); however, to the best of our knowledge, VHL status has not been prospectively validated as a predictive biomarker for treatment selection. Given the important role of VHL-HIF axis dysregulation in

Table IV. Key clinical trials of systemic therapies in advanced renal cell carcinoma.

Trial (NCT)	Regimen	Phase	n (comparison arms)	Median OS (months)	Median PFS (months)	ORR (%)	HR (OS)	HR (PFS)	(Refs.)
CheckMate 214 (NCT02231749)	Nivolumab + ipilimumab vs. sunitinib	III	1096	52.7 vs. 37.8 (ITT)	12.4 vs. 12.3 (ITT)	39.5 vs. 33.0 (ITT)	0.71 (ITT, final analysis)	0.88 (ITT)	(84,85)
KEYNOTE-426 (NCT02853331)	Pembrolizumab + axitinib vs. sunitinib	III	861	47.2 vs. 40.8	15.7 vs. 11.1	60.6 vs. 39.6	0.84	0.69	(5)
JAVELIN Renal 101 (NCT02684006)	Avelumab + axitinib vs. sunitinib	III	886	44.8 vs. 38.9	13.9 vs. 8.5	59.7 vs. 32.0	0.88	0.66	(86)
CLEAR (NCT02811861)	Lenvatinib + pembrolizumab vs. sunitinib	III	712 (355 vs. 357)	53.7 vs. 54.3	23.9 vs. 9.2	71.3 vs. 36.7	0.79	0.47	(6,87)
CheckMate 9ER (NCT03141177)	Nivolumab + cabozantinib vs. sunitinib	III	651	46.5 vs. 35.5	16.4 vs. 8.3	55.7 vs. 27.4	0.79	0.58	(8)
METEOR (NCT01865747)	Cabozantinib vs. everolimus	III	658	21.4 vs. 17.1	7.4 vs. 3.9	17.0 vs. 3.0	0.70	0.51	(73,74)
CABOSUN (NCT01835158; Alliance A031203)	Cabozantinib vs. sunitinib	II	157	26.6 vs. 21.2	8.6 vs. 5.3 (IR)	20.0 vs. 9.0 (IR)	0.80	0.48	(76)
Study 205 (NCT01136733)	Lenvatinib + everolimus vs. everolimus	II	101 (51 vs. 50)	25.5 vs. 15.4	14.6 vs. 5.5	43.0 vs. 6.0	0.51	0.40	(92)
LITESPARK-005 (NCT04195750)	Belzutifan vs. everolimus	III	746	21.4 vs. 18.1 (P=0.200NS)	5.6 vs. 5.6 (P=0.002)	21.9 vs. 3.5	0.88 (NS)	0.75	(20)
CheckMate 025 (NCT01668784)	Nivolumab vs. everolimus	III	821	25.0 vs. 19.6	4.6 vs. 4.4	25.0 vs. 5.0	0.73	0.88	(83)

For each trial, the source publications used for the tabulated efficacy data are explicitly identified. Where mature or final follow-up data were incorporated, the corresponding source publication is specified below. For CLEAR, data are from the final prespecified overall survival analysis by Motzer *et al* (87); the primary analysis was reported in (6). For METEOR, median PFS and ORR are from the primary analysis by Choueiri *et al* (73) and mature OS is from the long-term follow-up publication by Motzer *et al* (74). For CABOSUN, PFS by independent review and updated OS are from the 2018 updated analysis by Choueiri *et al* (76). For CheckMate 214, median OS, median PFS and ORR are reported from the 8-year analysis by Tannir *et al* (84), whereas the final 9.3-year analysis by Choueiri *et al* (85) provides the most mature OS hazard ratio (HR 0.71) and long-term survival estimates. NCT, ClinicalTrials.gov identifier; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; HR, hazard ratio; ITT, intent-to-treat population; NS, not significant; IR, independent review; CheckMate 214, Nivolumab + Ipilimumab vs. Sunitinib Trial; KEYNOTE-426, Pembrolizumab + Axitinib vs. Sunitinib Trial; JAVELIN Renal 101, Avelumab + Axitinib vs. Sunitinib Trial; CLEAR, Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma Trial; METEOR, Cabozantinib vs. Everolimus in Advanced Renal-Cell Carcinoma Trial; CABOSUN, Cabozantinib vs. Sunitinib in Metastatic Renal Cell Carcinoma Trial; Study 205, Lenvatinib + Everolimus Combination Trial; LITESPARK-005, Belzutifan vs. Everolimus for Advanced Renal-Cell Carcinoma Trial; CheckMate 025, Nivolumab vs. Everolimus in Advanced Renal-Cell Carcinoma Trial.

ccRCC pathogenesis, HIF-2 α inhibition with belzutifan is a mechanistically rational approach. However, translation from VHL-disease biology to sporadic ccRCC efficacy requires careful population-specific interpretation, as the clinical activity in VHL disease does not fully predict outcomes in sporadic metastatic RCC (20).

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk stratification integrates clinical and laboratory parameters (Karnofsky performance status, time from diagnosis to treatment, hemoglobin, calcium, neutrophil count and platelet count) to categorize patients into favorable, intermediate and poor risk groups (94). IMDC is an established prognostic model (94) and has subsequently been incorporated into multiple phase III RCC trials (4-6). However, whether IMDC risk independently predicts differential benefit from specific therapeutic classes (ICI combinations vs. TKI monotherapy) remains less certain, as cross-trial comparisons are inherently limited by population differences.

Key chromatin remodeling gene mutations provide additional prognostic information. BAP1 mutations associate with aggressive disease features and shorter OS (33,35). PBRM1 mutations show variable prognostic impact depending on co-occurring alterations; the association between PBRM1 alterations and immunotherapy response remains controversial, with conflicting data across different cohorts that likely reflect co-occurring mutations (especially BAP1), patient heterogeneity and assay differences (28-30). SETD2 mutations are associated with higher tumor grade and increased metastasis risk (37). PD-L1 expression has been evaluated as an adjunctive biomarker in several RCC trials; however, its predictive utility is inconsistent and it is not validated for stand-alone treatment selection (57).

First-line treatment selection is guided primarily by IMDC risk category and histological features. For patients of IMDC favorable-risk, TKI monotherapy, including sunitinib (11) or pazopanib (95), remains an active treatment option based on phase III evidence, particularly for patients with low disease burden, indolent disease behavior or contraindications to immunotherapy (7,11,95). Alternatively, ICI + TKI combinations (such as pembrolizumab + axitinib or nivolumab + cabozantinib) may be considered for patients of favorable-risk with high disease burden or rapid progression potential (5,8). The choice incorporates patient comorbidities, performance status and toxicity preferences. For patients of IMDC intermediate/poor-risk, dual ICI with nivolumab + ipilimumab offers durable long-term benefit; at 8-year follow-up, median OS was 46.7 months vs. 26.0 months with sunitinib (HR 0.69; 95% CI 0.59-0.81) (84). ICI + TKI combinations such as pembrolizumab + axitinib, nivolumab + cabozantinib and lenvatinib + pembrolizumab have produced high objective response rates in their respective phase III trials and may be considered when rapid tumor shrinkage is clinically important (5-8,57). However, to the best of our knowledge, no head-to-head trial directly compares dual ICI with ICI + TKI regimens and indirect response-rate comparisons across trials should therefore be interpreted cautiously. For non-clear-cell RCC, treatment selection should be histology-specific. In papillary RCC, cabozantinib has randomized phase II evidence from the SWOG 1500/PAPMET trial (96), whereas evidence for

other non-clear-cell histologies is more heterogeneous and enrollment in clinical trials is encouraged.

Upon disease progression, treatment selection is guided by the prior therapeutic context. After progression on VEGF-TKI monotherapy, cabozantinib has shown activity in clinical trials (multi-target TKI with MET/AXL inhibition) (73), nivolumab (ICI switch) (83), lenvatinib + everolimus (TKI + mTOR combination) (92) or tivozanib (selective VEGFR TKI) (77,78). The choice depends on prior TKI exposure, residual toxicity, and molecular features. After progression on ICI-based therapy, VEGF-directed TKIs remain important treatment options. Cabozantinib served as the active comparator in the phase III CONTACT-03 trial after prior ICI therapy, whereas the addition of atezolizumab to cabozantinib did not improve outcomes (97). Tivozanib represents another later-line VEGFR-directed option supported by phase III TIVO-3 data (78). Belzutifan (HIF-2 α inhibitor) is a mechanistically rational option after prior ICI and VEGF-TKI therapy, based on LITESPARK-005 results showing PFS benefit (20), though the absence of a statistically significant OS advantage at the reported analysis tempers enthusiasm for belzutifan monotherapy in this population.

Continuous monitoring enables treatment modification throughout the disease course. Among candidate biomarkers, PBRM1 remains investigational because associations with ICI response have been inconsistent across cohorts and may be influenced by co-occurring alterations such as BAP1 (28-30). BAP1 is more established as a prognostic marker associated with aggressive tumor biology than as a validated predictive marker for treatment selection (33,35). PD-L1 expression should not be used as a stand-alone treatment-selection biomarker in RCC because its predictive associations vary across therapeutic regimens, assay platforms and cut-off definitions (4,57). Circulating biomarkers, including circulating tumor (ctDNA) and circulating tumor cells (CTCs), also remain investigational; relatively low ctDNA shedding and the lack of prospectively validated treatment-adaptation algorithms currently limit routine clinical implementation. Systemic inflammatory markers such as NLR and CRP provide prognostic information in ICI-treated RCC cohorts, with elevated values generally associated with poorer outcomes (68). Standard radiographic assessment per RECIST remains the cornerstone of response evaluation, performed at regular intervals (typically every 8-12 weeks during active therapy) (7,98).

Multi-omics integration and precision medicine. RCC continues to pose challenges in oncology despite key therapeutic advances. The integration of multi-omics data, including genomics, transcriptomics, proteomics, metabolomics and spatial profiling, holds promise for unraveling the complex molecular landscape of RCC (67,99). Recent studies have highlighted the importance of genomic classification in RCC, emphasizing the need for personalized treatment strategies (67,99). Notably, a multi-omic analysis of 100 ccRCC cases integrating genomic, transcriptomic, proteomic, metabolomic and spatial data identified metabolic reprogramming associated with disease progression (99). Metabolomic analyses have revealed potential therapeutic targets and biomarkers. Single-cell omics approaches are emerging but remain

underexplored in RCC; their application resolves intra-tumor heterogeneity and clarifies differential therapeutic responses at the cellular level. By combining multi-omics datasets, including prospective single-cell profiling, researchers can develop more precise treatment plans tailored to individual patients.

Artificial intelligence and radiomics are emerging as complementary tools for precision oncology in RCC. Machine learning algorithms applied to radiomic features extracted from routine imaging may non-invasively predict molecular subtypes, treatment response and resistance patterns, though these approaches remain investigational and require prospective validation before clinical implementation (100,101).

Drug resistance: Mechanisms and clinical implications. Drug resistance in RCC follows distinct evolutionary patterns depending on the therapeutic class. Understanding these mechanisms informs rational treatment sequencing and the design of clinical trials evaluating novel combination approaches.

Resistance to VEGF-TKIs involves primary mechanisms (alternative pro-angiogenic signaling through FGF/PDGF, MET pathway activation and MDSC recruitment) (66) and acquired mechanisms (EMT, alternative angiogenic factor upregulation and vessel co-option). Collectively, VEGF resistance reflects adaptive vascular rewiring rather than linear pathway escape, explaining why sequential VEGF-directed strategies and combination approaches targeting parallel axes (ICI, HIF-2 α) have become necessary.

Resistance to ICIs reflects both tumor-intrinsic and microenvironmental factors. An important challenge is that RCC employs multiple redundant immune evasion mechanisms, antigen loss, T-cell exhaustion and alternative checkpoint upregulation, meaning no single intervention is likely to restore immune control in resistant disease. Primary resistance involves an immunologically ‘cold’ phenotype with defective antigen presentation and an immunosuppressive microenvironment (56). Acquired resistance develops through T-cell exhaustion, antigen loss through immunoeediting, and compensatory checkpoint upregulation (56). Strategies intended to limit or circumvent primary immune resistance include dual checkpoint blockade and ICI-TKI combinations (4,6). However, these first-line trials do not establish reversal of acquired ICI resistance and to the best of our knowledge, no strategy has shown consistent efficacy in reversing established resistance. Novel targets such as lymphocyte activation gene 3 (LAG-3) and T-cell immunoreceptor with Ig and ITIM domains (TIGIT) therefore remain under investigation.

Resistance to HIF-2 α inhibition remains incompletely characterized. Translational studies with the first-generation HIF-2 α inhibitor PT2385 identified an acquired EPAS1/HIF-2 α G323E gatekeeper mutation that interfered with drug binding and preserved HIF-2 complex formation, providing evidence for on-target acquired resistance in ccRCC (102). Additional HIF-independent or alternative clonal escape mechanisms remain under investigation. Belzutifan-based combinations are being explored clinically. Notably, LITESPARK-011 has now reported phase III results demonstrating improved PFS with belzutifan + lenvatinib vs. cabozantinib after prior anti-PD-L1

therapy (90), whereas other belzutifan-based combination strategies remain investigational.

Potential cross-class interactions merit consideration. VEGF-pathway inhibition can exert immunomodulatory effects and may alter the tumor microenvironment in ways that could influence subsequent ICI activity (103,104). Conversely, VEGF-directed TKIs retain clinical activity in selected patients after ICI progression, as illustrated by the cabozantinib comparator arm in CONTACT-03 (97). These observations are hypothesis-generating and prospective evidence defining optimal cross-class sequencing remains lacking (Fig. 3).

Controversies, unresolved questions and evidence limitations.

A number of therapeutic approaches that once appeared promising have not yet established durable roles in RCC clinical practice. Everolimus was commonly used as second-line therapy after the RECORD-1 trial demonstrated PFS benefit vs. placebo (9), but nivolumab (83) and cabozantinib (73) have largely replaced it in this setting based on improved OS data. Everolimus monotherapy now has a limited role except in specific contexts where immunotherapy is contraindicated. Although TIVO-1 did not establish tivozanib as a broadly adopted first-line standard, subsequent TIVO-3 data supported its role as a later-line option in previously treated advanced RCC (77,78). Thus, tivozanib is better viewed as a VEGFR-selective later-line therapy rather than as a failed therapeutic strategy. FGFR inhibitors, including erdafitinib (105), have demonstrated activity in urothelial carcinoma but lack RCC-specific phase III evidence; extrapolation from other tumor types is not supported by current evidence without dedicated trials. Imatinib was evaluated directly in metastatic RCC, but a small phase II study reported no objective responses among 12 evaluable patients, illustrating the limited clinical translation of KIT/PDGF receptor-directed therapy in unselected RCC populations (106).

The biomarker landscape in RCC remains marked by inconsistency and limited clinical utility. PBRM1 mutations illustrate this challenge: A number of studies suggest enhanced ICI benefit while others demonstrate resistance (28-30). This controversy likely reflects co-occurring mutations (especially BAP1), patient heterogeneity, differences in assay platforms and varying analytical approaches across cohorts. No consensus exists on the clinical utility of PBRM1 as a predictive biomarker and its use in routine treatment selection is not supported by prospective data. Overall, no single biomarker has achieved sufficient consistency and prospective validation to guide routine clinical decision-making in RCC. PD-L1 expression was incorporated into prespecified analyses in trials such as JAVELIN Renal 101 (57), but its predictive value has not been consistent across RCC trials. CheckMate 214 showed benefit regardless of PD-L1 status (4) and it is not validated as a stand-alone treatment-selection biomarker. These discordant results limit routine clinical use and PD-L1 remains an adjunctive rather than definitive predictive marker. VHL is a central pathway-defining alteration in ccRCC, but its clinical predictive value for selecting among anti-angiogenic therapies remains unvalidated; routine VHL testing to guide TKI selection has not been adopted (12,50). ctDNA holds promise in other malignancies for response monitoring and resistance detection, but RCC-specific validation is lacking

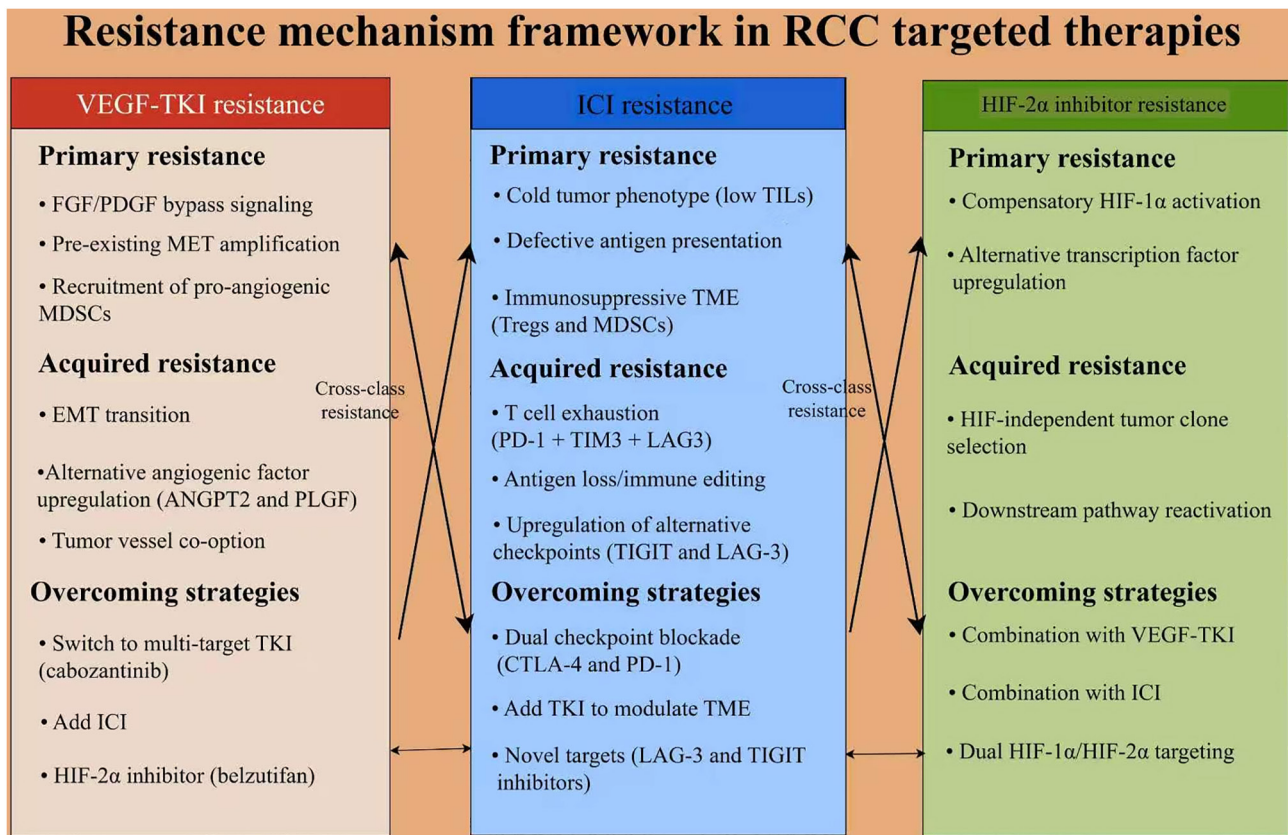


Figure 3. Resistance mechanisms across systemic therapies in RCC. Schematic overview of resistance mechanisms to VEGF-TKIs, ICIs and HIF-2 α inhibitors in RCC. VEGF-TKI resistance arises from FGF/PDGF bypass signaling, MET pathway activation, MDSC-driven angiogenesis and acquired EMT with compensatory pro-angiogenic factors (such as ANGPT2 and PLGF) and vessel co-option (66). ICI resistance is mediated by a non-inflamed ('cold') tumor microenvironment, defective antigen presentation and immunosuppressive infiltrates (Tregs and MDSCs), while acquired escape involves T-cell exhaustion (PD-1/TIM-3/LAG-3), immune editing and alternative checkpoint upregulation (TIGIT and LAG-3) (56). HIF-2 α inhibitor resistance includes acquired EPAS1/HIF-2 α gatekeeper mutations (such as G323E, reported with the first-generation inhibitor PT2385) and potential HIF-independent clonal escape; these mechanisms remain incompletely defined and are based partly on translational and preclinical evidence (102). Potential cross-class adaptation and sequencing interactions reflect dynamic therapeutic interdependence across angiogenic, immune and hypoxia-driven axes (103,104). Potential or investigational strategies include multi-target TKIs (such as cabozantinib), ICI-based combinations (CTLA-4/PD-1 blockade), VEGF-ICI dual targeting and next-generation HIF-2-directed approaches. Figure created with Figdraw (www.figdraw.com). RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; HIF, hypoxia-inducible factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; MET, mesenchymal-epithelial transition factor; MDSC, myeloid-derived suppressor cell; EMT, epithelial-mesenchymal transition; ANGPT2, angiopoietin 2; PLGF, placental growth factor; Treg, T regulatory cell; PD-1, programmed cell death protein 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; LAG-3, lymphocyte-activation gene 3; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; EPAS1, endothelial PAS domain protein 1.

due to lower tumor shedding rates and no prospective data support ctDNA-guided treatment adaptation in RCC.

From a clinical implementation perspective and consistent with the aforementioned biomarker-specific assessment, none of these molecular biomarkers currently provide sufficient prospective evidence for routine treatment selection in RCC. PBRM1, BAP1, PD-L1 and circulating biomarkers such as ctDNA and CTCs all remain investigational for treatment selection and their predictive utility requires prospective validation in dedicated clinical trials.

Numerous mechanistic assumptions underlying RCC therapy have been challenged or tempered by clinical evidence. The assumption that 'VEGF inhibition alone is sufficient' has been challenged by the rapid emergence of resistance to single-agent VEGF-TKIs and the subsequent need for multi-target TKIs and combination approaches, though even these more intensive strategies demonstrate limited long-term durability, highlighting the adaptive capacity of RCC. The assumption that 'immunotherapy benefit is independent of VEGF' has been challenged

by ICI + TKI combination data showing improved outcomes to historical ICI monotherapy data (5,6,8), though to the best of our knowledge, no direct ICI vs. ICI + TKI head-to-head trials exist to conclusively address this question. The assumption that 'HIF-2 α inhibition translates directly from VHL-disease to sporadic RCC' has been tempered by LITESPARK-005, which demonstrated a PFS benefit, whereas OS did not meet the prespecified statistical-significance criterion at the reported analysis in a heavily pretreated population (20), suggesting that the mechanistic rationale, while sound, may not fully capture the complexity of treatment-resistant sporadic disease. Finally, the concept of 'EMT as a therapeutic target', despite extensive preclinical literature (66,107), lacks sufficient prospective validation in RCC, EMT is a descriptive biological process rather than a validated therapeutic target in RCC.

Evidence grading limitations should be acknowledged when interpreting the RCC literature. Numerous biomarker claims that are often cited as high-level evidence derive from post hoc subgroup analyses of phase III trials rather than from

prospectively designed biomarker-stratified studies. This distinction is key, as post-hoc analyses are hypothesis-generating rather than hypothesis-confirming and their findings require prospective validation before clinical implementation. The IMDC prognostic model was established prospectively and validated across multiple trials, but its predictive value for guiding treatment selection (as opposed to prognosis) is less certain. Cross-trial comparisons are inherently limited by differences in patient populations, eligibility criteria, assessment methodologies and follow-up durations, yet such comparisons frequently appear in the literature and should be interpreted with caution. Real-world patient populations are often excluded from pivotal trials, including those with brain metastases, poor performance status and non-clear cell histology, limiting the generalizability of trial findings to the broader RCC population. These limitations underscore the need for prospective biomarker-embedded trials and real-world evidence studies to complement the existing randomized controlled trial data.

Liquid biopsy and real-time monitoring. Liquid biopsy technology (108), involving analysis of CTCs, cell-free DNA and exosomes (109), offers a non-invasive alternative for RCC diagnosis, prognosis and treatment monitoring. Cell-free DNA analysis can detect actionable mutations, monitor treatment response and identify emerging resistance mechanisms in real time. However, RCC exhibits lower baseline ctDNA shedding rates compared with malignancies such as lung or colorectal cancer, which may limit the sensitivity of ctDNA-based monitoring in this disease. Numerous studies have demonstrated the feasibility of liquid biopsy in RCC (108–110), though prospective validation and standardization in RCC remain ongoing challenges. Integration of liquid biopsy into clinical practice could enable dynamic treatment adaptation and early intervention at progression, pending prospective RCC-specific validation.

Novel therapeutic targets and future directions. The RCC therapeutic landscape continues to evolve with investigation of novel targets. HIF-2 α inhibition with belzutifan may represent an emerging targeted approach directed at the important VHL-HIF axis (19,111). Additional belzutifan-based combination strategies remain investigational and belzutifan + lenvatinib has now demonstrated a PFS benefit over cabozantinib in the phase III LITESPARK-011 trial (90). In the adjuvant setting, LITESPARK-022 further extends this strategy by combining HIF-2 α inhibition with PD-1 blockade; pembrolizumab + belzutifan notably improved disease-free survival compared with pembrolizumab alone, although OS data remain immature (91). Other investigational approaches include novel immunotherapy combinations such as LAG-3, TIGIT and T-cell immunoglobulin and mucin-domain containing-3 inhibitors, tumor-infiltrating lymphocyte therapy and chimeric antigen-T cell approaches; antibody-drug conjugates targeting RCC-specific antigens; and metabolic pathway inhibitors targeting glycolysis, glutaminolysis and lipid synthesis. The integration of these novel approaches with established targeted and immunotherapy agents may further improve outcomes for patients with advanced RCC.

Future directions in RCC research. The RCC therapeutic landscape continues to evolve rapidly. Numerous areas warrant

particular attention in future research. First, the development of predictive biomarkers capable of guiding treatment selection beyond IMDC risk stratification remains a key unmet need. Prospective validation of circulating tumor DNA, radiomic signatures and multi-omic integrative platforms may enable dynamic treatment adaptation. Second, further phase III validation, mature OS follow-up and prospective sequencing studies are needed for HIF-2 α -based combination strategies, while novel checkpoint targets such as LAG-3 and TIGIT require dedicated prospective clinical evaluation. Third, treatment approaches for non-clear cell RCC histologies and patient populations underrepresented in clinical trials demand dedicated investigation and careful prospective trial design will be essential to validate these emerging strategies (112).

6. Conclusion

RCC treatment has transitioned from cytokine-based therapy to a multidimensional strategy integrating targeted therapy and immunotherapy. Current evidence supports VEGF-TKIs and ICI-based combinations as the backbone of first-line treatment, particularly in advanced clear cell RCC. However, treatment selection remains largely driven by clinical risk stratification rather than validated predictive biomarkers. Although genomic and transcriptomic alterations such as VHL, PBRM1 and BAP1 provide mechanistic insight, their clinical utility in guiding therapy remains limited. In addition, the absence of head-to-head trials comparing these regimens requires treatment selection based on IMDC risk, comorbidity profiles and toxicity considerations rather than a universal first-line standard. Resistance to therapy arises through interconnected angiogenic, immune and metabolic pathways, highlighting the need for combination strategies and longitudinal disease monitoring. Future progress will depend on prospective biomarker-driven trials, integration of multi-omic datasets and development of adaptive treatment strategies capable of addressing tumor heterogeneity and evolutionary resistance. Resistance to targeted and immunotherapy agents follows distinct class-specific mechanisms with potential cross-class interactions, yet validated sequencing strategies remain undefined. Understanding why some biologically rational strategies show limited durability or context-dependent benefit, such as single-pathway VEGF blockade, EMT-directed approaches and HIF-2 α monotherapy in heavily pretreated disease, may inform rational trial design more effectively than incremental additions to existing frameworks.

RCC is increasingly recognized as a complex disease with multiple interacting biological processes, rather than a purely VEGF-driven malignancy. Therapeutic strategies in RCC address several biologically relevant pathways, including angiogenesis (VHL/HIF/VEGF), immune modulation (checkpoint response) and chromatin remodeling (PBRM1/BAP1/SETD2), though the relative importance of each varies across individual tumors. Progress in the field will depend on integrating multi-dimensional molecular data across these axes to enable dynamic treatment adaptation rather than static biomarker classification. Future progress will depend on prospective biomarker-embedded trials, standardized comparison methodologies and investigation of underserved populations. The goal is to move toward more individualized treatment approaches, with molecular monitoring informing

treatment selection where evidence supports such integration. Advances in multi-omic profiling, liquid biopsy technology and mechanism-informed combination design offer potential for improving RCC treatment approaches.

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Availability of data and materials

Not applicable.

Authors' contributions

HC, YX and ZZ were responsible for the conception of the present study. HC, YX, ZZ and HS were responsible for literature retrieval, screening and evaluation. JS and PY were responsible for the design and preparation of Figs. 1-3 and Tables I-IV, and drafted the corresponding sections of the manuscript. YuL and GZ contributed to literature screening, data extraction and verification of the references list, and participated in drafting the manuscript text. AT and JC participated in the production of the figures and the collection of the literature, and AT also participated in drafting the manuscript text. YaL contributed to the language polishing and formatting of the manuscript, and revised the manuscript for grammar and style. HS critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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