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Review

Non-Clear Cell Renal Cell Carcinoma: Molecular Pathogenesis, Innovative Modeling, and Targeted Therapeutic Approaches

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Abstract: Non-clear cell renal cell carcinomas (nccRCC) are a diverse group of kidney cancers with histopathologically and genetically heterogeneous features. About 25% of renal cell carcinomas (RCCs) are nccRCC types. The management and treatment of nccRCCs are rather limited, and the data are often estimated from studies in the more common clear cell renal cell carcinoma (ccRCC). Each subtype has its own distinctive biological and therapeutic profile. Our knowledge of the underlying biological features of nccRCC has directed and continues to shape the use of novel therapy targeting the main signaling pathways and leading to improved overall survival (OS) of the patients. This review discusses the characteristic molecular features of the major types of nccRCC and current cell-based and animal models for studying them. In the following, we highlighted major signaling pathways and therapeutic approaches for nccRCC patients.

Keywords: collecting duct carcinoma; papillary renal carcinoma; hybrid oncocytic tumors; renal medullary cell carcinoma

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1. Introduction

Renal cell carcinomas (RCCs) account for approximately 85% of all primary kidney tissue neoplasms [1]. Overall, incidence rates in men are usually higher than in women. RCCs are a heterogeneous group of cancers related to different histological characteristics, time of development of metastatic disease, genetic drivers, mutational load, and response to currently available therapies [2]. Renal tumors are classified into subtypes based on morphology, cell of origin, and pathological features, including cytoplasmic characteristics in clear-cell RCC (ccRCC; 80%) and chromophobe RCC (chRCC; 5%), architectural structure in papillary RCC (pRCC; 15%), anatomical origin (very rare collecting duct versus renal medullary carcinomas), oncocytic or cystic disease-associated RCCs (less than 1%), molecular pathognomonic alterations (microphthalmia transcription factor family translocation carcinomas and succinate dehydrogenase (SDH)-deficient renal carcinomas), or familial predisposition syndromes (hereditary leiomyomatosis and RCC syndrome-associated renal cancer) [3,4].

Clear-cell RCC originates from the proximal tubular epithelial cells (renal cortex). Clear-cell RCC cells are characterized by lipid-rich ample cytoplasm (neoplasm). CcRCC is the most common histological type of kidney cancer, and management and treatment of nccRCCs are often based on extrapolating data from therapeutic experiences with ccRCC [5].

1.1. Non-Clear RCC

The major common non-clear cell subtypes of RCC include papillary, chRCC, collecting duct, medullary, translocation associated, and unclassified. The prognosis of and efficacy of therapeutic options for nccRCCs are based on extrapolation methods from the clinical assessment used for more common ccRCC [6]. In the following sections, we will describe the characteristic features of the major types of nccRCC, as well as the current cell-based and animal models for studying them. Table 1 lists cell lines of different subtypes of nccRCC.

Table 1. Cell lines of different subtypes of non-clear cell renal cell carcinoma (nccRCC).

Subtype of nccRCC	Cell Lines
pRCC	ACHN, Caki-2, UOK112, UOK268, UOK342, UOK275, SKRC-39, NCCFH1, and UOK262
Chromophobe RCC	UOK276
RMC	UOK353, UOK360

Abbreviations: nccRCC: non-clear cell renal cell carcinoma, pRCC: Papillary renal cell carcinoma, RMC: Renal medullary cell carcinoma, RCC: Renal cell carcinoma.

1.2. Papillary Renal Cell Carcinoma (pRCC)

Papillary renal cell carcinoma (pRCC) originates from the proximal and distal convoluted tubular cells [5]. pRCC is the second most common renal cell carcinoma (RCC) subtype and accounts for 15–20% of all kidney neoplasms [2]. pRCC has a higher 5-year cancer-specific survival rate than ccRCC (94.5% versus 86.9%). pRCC patients have a more favorable outcome following surgical treatment compared to patients with clear RCC (ccRCC). Furthermore, pRCCs are associated with less aggressiveness and exhibit less development of distant metastasis and recurrence [7]. pRCCs are subclassified into two subtypes based on the morphological characteristics and cytogenetic background affecting patient survival. Lesions in patients with type 1 pRCC are often multifocal at primary diagnosis. These tumors have papillae and tubular structures (single layer) with delicate fibrovascular cores surrounded by small basophilic cells with scares cytoplasm and oval nuclei. These cells organize in a spindle-shaped pattern. Type 2 pRCC is more heterogeneous than type 1 pRCC and is characterized by papillae covered by large cells containing eosinophilic granular cytoplasm and large, pseudostratified nuclei with prominent nucleoli [2]. These cancers occur sporadically or as a part of a hereditary cancer-predisposing disease. Both subtypes are associated with specific genetic alterations with differences in patient survival [8]. The genetic basis of pRCC is mainly based on studies of the inherited form of the disease. Hereditary pRCC is a rare autosomal dominant disorder in which patients usually have multiple renal tumors and are at risk for developing type 1 papillary RCC. Genetic linkage analysis in HPRC families revealed that the pathologic gene is localized on chromosome 7q31 [9,10]. Type 1 pRCC is characterized by mesenchymal to epithelial transition (hepatocyte growth factor receptor, *MET*) proto-oncogene alterations or variations on chromosome 7, and type 2 pRCC has alterations in *CDKN2A*, *SETD2*, *BAP1*, *PBRM1*, *FH*, *NF2*, *TFE3*, *NFE2L2*, and *ARE* genes [11]. Type 1 pRCC has a better prognosis and outcome compared to the more aggressive type 2 tumors [12].

Inherited mutations are a potential risk factor for *pRCC* and represent a major challenge because appropriate models to study this cancer development are limited. Figure 1 summarizes the various types of *in vitro* (Figure 1a) and mouse models (Figure 1b) for studying various types of nccRCC. Several cell lines with a papillary histotype are widely

used to study pRCC. ACHN, a commercial cell line, was established from malignant pleural effusion from a patient with metastatic RCC. These cells have the main genetic and molecular characteristics of pRCC, such as the lack of von Hippel–Lindau (*VHL*) mutations [13,14] and the presence of c-*MET* polymorphism [14,15]. Several studies developed the sunitinib-resistant subline of the ACHN cells (ACHN/RSu) and the temsirolimus-resistant subline of ACHN cells (ACHN/Rte) in the presence of increasing concentrations of these drugs [16]. Other cell lines used as models for pRCC are Caki-2, UOK112, UOK268, UOK342, UOK275, NCCFH1, and UOK262 [17–21]. Molecular and histological examination of Caki-2 cells indicated that these cells have the characteristics of type 2 pRCC, including overexpression of *MET* and *LRRK2,* ARE-controlled genes, and chromosome 8 aberrations [20,22,23]. Furthermore, *VHL* mutations (a clear-cell characteristic) have been reported in Caki-2-derived xenografts and several patients with pRCC. Nevertheless, based on the genetic and molecular analysis and histological assessment of Caki-2, it is considered as a model of papillary-type kidney tumors [24,25]. In addition to Caki-2, the UOK112 and UOK268 cell lines were also established from a primary kidney tumor [18,19,21]. UOK342 and UOK275 are pRCC patient-derived cell lines with a mutation in the *NF2* gene [26]. NCCFH1 is a cell line with mutations in the *MET* and *FH* genes or overexpression of ARE-controlled genes [21]. The UOK262 cell lines were derived from a retroperitoneal metastasis in a patient with RCC [18,19,21].

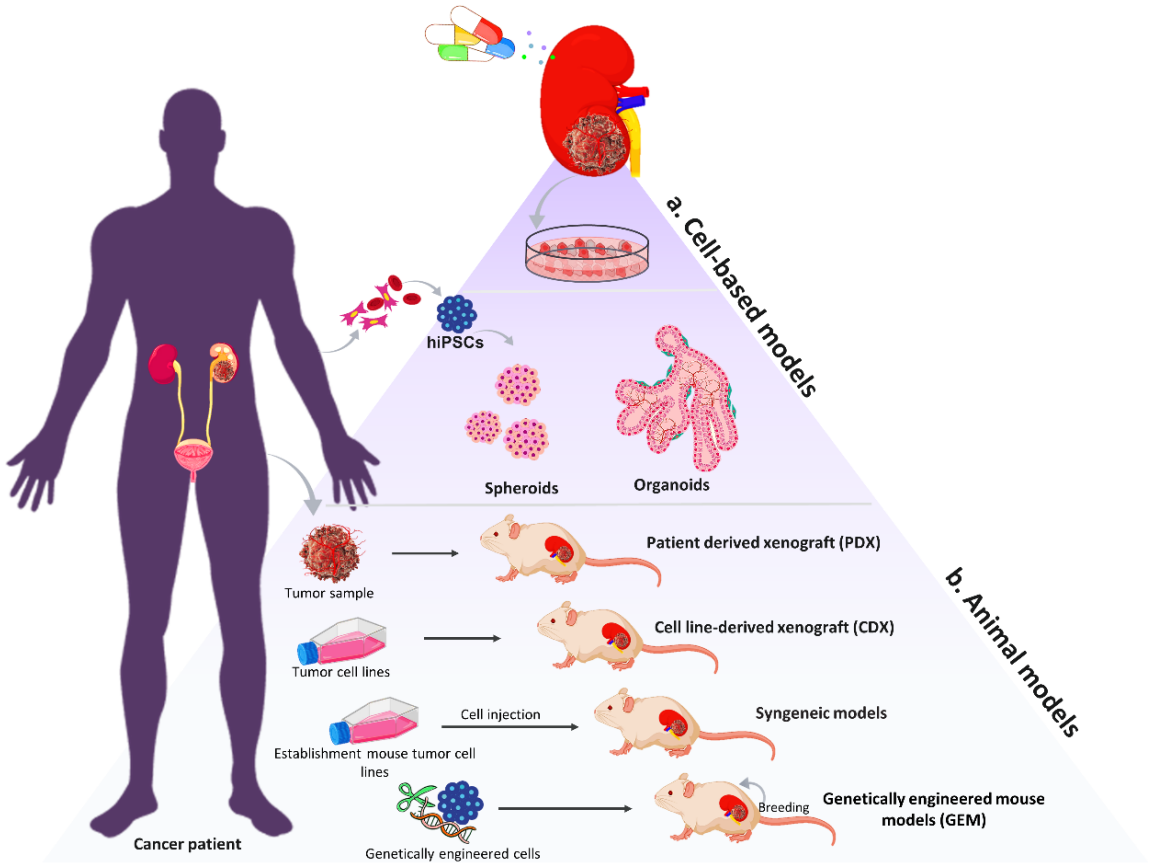

Figure 1. Summary of the various types of *in vitro* (**a**) and mouse models (**b**) for studying nccRCC.

The use of cell lines for cancer modeling has several limitations. Although the c-Met receptors found in human tumor tissue are over-expressed and highly active, those expressed on the surface of conventional two-dimensional (2D) cultured pRCC cells are only weakly activated. Furthermore, these cells fail to respond functionally to c-Met inhibitors [27]. On the other hand, tumors consist of not only cancerous cells but also the tumor's microenvironment, immune system, and endothelial cells. Therefore, homogeneous cell lines do not

accurately represent cell–cell interactions and physical/chemical stimuli prepared by the tumor's microenvironment. Experiments on drug resistance performed on the cancerous cell lines underestimate mechanisms associated with the other essential cell types such as endothelial and immune cells [2]. In recent years, 3D co-culture systems were developed and provided highly physiological systems and a more sophisticated platform for disease modeling and drug screening [28,29]. Recently, Rosette and colleagues developed a 3D co-culture system in which pRCC tumor cells are layered on top of the primary fibroblasts to recapitulate the papillary architecture of pRCC tumors. This 3D spheroid model is sensitive to capmatinib, a highly potent and selective inhibitor of the MET receptor [27].

Animal models are widely used in pRCC research. There are genetically engineered mouse models (GEM) to study mechanisms involved in pRCC tumor development and their therapeutic approaches (Figure 1b). Bailey and colleagues developed a mouse model and showed that combined MYC activation and Vhl and Cdkn2a (Ink4a/Arf) deletion (VIM) resulted in kidney tumors with type 2 pRCC histology [30]. Calcagni and colleagues established a transgenic mouse model with kidney-specific transcription factor EB (TFEB) overexpression. This model had kidney tumors with a mixture of ccRCC and type 2 pRCC histology. Transcriptome analysis reveals that Wnt signaling has a central role in the pathogenesis of this type of RCC tumor [31]. Another study established a renal-specific knockout mouse model by disrupting the mouse Flcn in the proximal tubules of the kidney. This tumor model consists of multiple histological types of RCC, including chRCC in mice under 12 months of age and pRCC within the kidneys of older ages. The mammalian target of rapamycin (mTOR) and transforming growth factor-β (TGF-β) signaling pathways were upregulated in the Flcn knockout model and had a critical role in the tumorigenesis [32]. Studies on animal models offer superior physiological models; however, they are not ideal due to the ethical concerns and interspecific differences [33].

Tumor xenograft models are essential approaches to research the pathogenesis and treatment of RCC. Xenografts can be derived from cell lines, named cell line-derived xenografts (CDX), or obtained from RCC patients, called patient-derived xenografts (PDX) (Figure 1b). These models, in terms of histology and genetic alterations, have remarkable similarities with clinical situations and are a good choice for studying the roles of the immune cells and tumor microenvironment [34]. ACHN, Caki-2, and SKRC39 cell lines are the most commonly used cell lines for the generation of CDX models to study pRCC. CDX models generated reproducible carcinomas closely resembling human pRCC with cystic papillary structures and vascularized networks. These models could be a suitable research approach to studying pRCC pathogenesis and investigating anti-cancer therapies [35–37]. PDX models were obtained from biopsy samples of tumor specimens of pRCC patients. Two PDX models included RCC-47 from a primary pRCC tumor and RCC-43b from a metastatic pRCC patient. These PDX models supported the pharmaco-dynamic and antitumor activity of a MET inhibitor, AZD6094 (Savolitinib) [38]. Another study showed that the PDX models could recapitulate the molecular genetics and drug responsiveness of RCC tumors in the clinical situation. In this study, dovitinib, sunitinib, and sirolimus were able to inhibit tumograft growth [39].

Novel kidney models, such as organoids, enable the precise analysis of the influence of specific genetic or molecular alterations on the development of drug resistance, including the effect of the tumor microenvironment [29,40]. Hwang and colleagues established an *in vitro* model of c-*met*-mutated hereditary kidney cancer. First, they generated human inducible pluripotent stem cells (hiPSCs) from cord blood mononuclear cells (CBMCs) of a patient with c-*met*-mutated type 1 PRCC. The c-*met*-mutated iPSCs spontaneously differentiated into the kidney organoids with glomeruli and proximal tubules in 3D culture conditions. These kidney organoids expressed renal-specific progenitor markers. This 3D kidney organoid was subsequently transplanted under the kidney capsule of an NSG mouse. Four weeks after transplantation, the researchers observed that the kidney organoids derived from c-*met*-iPSCs formed larger tumors compared to the control groups. These organoids displayed an aberrant gene expression signature that was highly associated with

the expression pattern found in a large cohort of PRCC patient samples. The researchers identified 11 common genes, including *BHLHE40* and *KDM4C,* which are factors involved in the PRCC pathogenesis [41].

1.3. Renal Chromophobe Cell Carcinomas and Oncocytomas

ChRCC is the third common (5–7% of all RCC) and less aggressive nccRCC subtype originating from the intercalated cells of the collecting duct system. The chRCC is an unencapsulated mass with pale tan to dark brown cut surfaces that is composed of two tumor cell types: pale cells and eosinophilic cells. The pale cells are large and polygonal with distinct cellular borders, reticulated cytoplasm, and perinuclear halos. In some cases, the cytoplasm is eosinophilic and microvesiculated. The eosinophilic cells are smaller and characterized by dense eosinophilic or granular cytoplasm [5].

Major molecular characteristics of chromophobe carcinomas are hypodiploidy affecting most or all of chromosomes 1, 2, 6, 10, 13, 17, or 21 (approximately 80% of these tumors) as well as a low number of exonic somatic mutations [42]. Furthermore, chRCC may result from rearrangements in the telomerase reverse transcriptase (TERT) promoter that lead to telomerase upregulation [43]. Several studies indicated that patients with chRCC may have mutations and alterations in proto-oncogenes such as *p53* (32% of cases), *KIT* as well as mTOR pathway (*TSC1* or *TSC2*) genes. These pathways could be therapeutic approaches in chRCC patients [43–45]. In addition, some autosomal dominant disorders are associated with a higher incidence of chromophobe renal tumors, including Birt-Hogg-Dubé (BHD) and Cowden syndromes with mutations in the *Follculin* and *PTEN* genes, respectively. It has been noted that mutations in *TP53* and *PTEN* are the two most common gene mutations, and mutations in *TSC1* or *TSC2* are the less common ones [46]. Metabolic pathway analysis of RCC subtypes showed that chRCC has a disturbance in metabolic pathways, including aspartate and glutamine anaplerosis biosynthesis [47]. Moreover, these tumors may display increased mitochondrial DNA (mtDNA) numbers and frequent mutations in mitochondrial genes. Mitochondrial gene mutations are also found in a subset of renal oncocytomas, which supports the finding that these subtypes of chRCCs may develop from oncocytomas [48–50]. Renal hybrid oncocytic/chromophobe tumors are a rare group of RCCs that have mixed histological characteristics of both oncocytoma and chRCC. However, genomic profiles of hybrid oncocytic/chromophobe RCCs revealed heterogeneity in genetic and molecular features [51].

Few cell lines are isolated from chRCCs that are not well-characterized and not commonly used for chRCC studies [52–54]. In 1995, researchers established two divergent permanent cell lines (chrompho-A and chrompho-B) from the chRCC of an 83-year-old female patient. Unfortunately, these cell lines failed to form tumors after sub-renal capsule transplantation in nude mice [52]. Yang and colleagues established a chRCC-derived immortal cell line model, UOK276, from a large chRCC tumor with regions of sarcomatoid differentiation. This cell line exhibited a *TP53* missense mutation that is commonly seen in chRCC. The UOK276 cell line was subcutaneously injected into athymic nude mice to evaluate the tumorigenic potential in a CDX model. The xenografts grew rapidly within 50 days after injection. The result showed that this cell line might be isolated from the segments of tumors that had undergone sarcomatoid differentiation (with large spindled, pleomorphic cell morphology). Consequently, UOK276 provides a unique *in vitro* and *in vivo* preclinical model for studying the deregulated pathways and testing therapeutic strategies in sarcomatoid differentiated chRCC [54].

chRCC tumors are the most common kidney tumors found in Birt-Hogg-Dube (BHD) syndrome patients. In BHD syndrome, almost all mutations are frameshift or nonsense mutations in the tumor-suppressor folliculin (*FLCN*) gene, leading to a nonfunctioning truncated BHD protein. Understanding the role of the *FLCN* gene in chRCC development sheds light on the generation of FLCN gene knockout in animal models. Two research groups established heterozygous mouse models (Ksp-Cre; FLCNΔ/-). They observed that these mice had enlarged polycystic kidneys with histological characteristics similar

to hybrid oncocytic/chromophobe RCCs. Molecular analysis showed that targeted *FLCN* knockout activated Akt-mTOR, Raf-extracellular signal-regulated protein kinase (Erk)1/2, and TGF-β signaling pathways in the kidneys [32,55]. *In vivo* models along established cell lines could be used to study many aspects of the chRCC biology and drug response.

1.4. Collecting (Bellini) Duct Renal Cell Carcinoma

Bellini duct carcinomas originating from the principal cells of the distal convoluted tubule section constitute only 1–2% of all RCC cases. This kidney tumor subtype is more common in males and usually occurs in young and middle-aged patients. Collecting duct carcinomas are aggressive kidney neoplasms with low survival rates, high rates of metastasis, and poor prognosis. Therefore, patients with CDC are diagnosed at an advanced stage [5,12]. Distant metastases to lymph nodes, bone, liver, and soft tissues occurred in 40% of these patients [56]. Histological analysis showed irregular, infiltrating cells that were arranged in the collecting duct walls along with interstitial inflammatory fibrosis and collagen secretion (desmoplasia) [5,57]. Cancerous cells in larger lesions have outward expansive growth and infiltrate into the renal pelvis and cortex [58]. CDC tumors are characterized by dilated tubules and papillary structures surrounded by simple cuboidal epithelium and marked desmoplasia [59]. Hematuria is present in about 84.6% of Bellini duct carcinoma patients [5,57]. Cytogenetic analysis has shown loss of heterozygosity of chromosomes 1q, 8p, and 13q in these patients associated with higher stage and poor clinical outcomes, thus, tumor suppressor genes on these regions may be involved in the pathogenesis of Bellini duct carcinomas [60,61]. The most common genomic alterations occurred in NF2 (29%), SETD2 (24%), and SMARCB1 (18%) [62]. *In vitro* culture of primary Bellini duct carcinomas cells showed that these cells expressed keratins 5, 8, and 18. Furthermore, these cells expressed erbB-1 oncogene, unlike ccRCC cells [63].

To the best of our knowledge, there are no particular *in vitro* cell lines for Bellini duct carcinomas. There is only the autochthonous transgenic animal model to study the Bellini duct carcinoma subtype. Shroff and colleagues established a transgenic mouse model with conditional overexpression of *Myc* oncogene using the Tet-on system. *Myc* expression was driven by the kidney-specific γ-glutamyl transferase (GGT) gene promoter linked to the tetracycline transactivator (*tTA*) gene. Induction of *Myc* with doxycycline (DOX) resulted in the fast development of highly aggressive Bellini duct carcinoma tumors. These tumors have the features of highly aggressive Bellini duct carcinomas, such as expression of E-cadherin, PAX8, CK5/6, and CK7 markers. This model could be used to evaluate new therapeutic approaches for the treatment of Bellini duct carcinomas [64]. Due to the invasive nature and limited numbers of cases, the only treatment options have been mainly extrapolated from the therapeutic options studied in other subtypes of RCC, including mTOR inhibitors and anti-angiogenic drugs.

1.5. Renal Medullary Cell Carcinoma (RMC)

Medullary RCC is a rare, extremely aggressive variant of RCC that predominantly occurs in patients of younger age (the second and third years of life) and is associated with African or Mediterranean descent with sickle cell disease or with heterozygous carriers of the sickle cell allele [65]. The majority of RMC patients with advanced disease usually develop metastases within the lymph nodes and lung and have an overall survival (OS) of less than 1 year. Medullary carcinoma is characterized by an irregular arrangement of cells with remarkable pleomorphism and hyperchromatic nuclei. Medullary carcinoma cells originate from the distal nephron [5]. Imaging studies of this solid hypovascular tumor showed infiltrating heterogeneous lesions that lead to calyceal obstruction and dilatation. Microscopically, experiments indicated necrosis areas with micropapillary patterns associated with polymorphonuclear leukocytes [66]. Given the rarity of RMC, the genetic features of this subtype are poorly understood. Studies indicated that RMC tumors often harbor translocations and deletions of tumor suppressor SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (*SMARCB1)*

or rearrangement in anaplastic lymphoma kinase (ALK) [67]. The absence of SMARCB1 protein in RMC leads to activation of the c-MYC pathway and subsequently induction of high levels of DNA replication stress, which results in the upregulation of cell-cycle checkpoint pathways [68]. The presence of a *BCR/ABL* rearrangement was reported in one study. No additional reports have been published that support this finding, and there is an urgent need for the development of preclinical models of RMC to expand knowledge of the pathogenesis mechanisms of this disease and find a proper therapeutic approach [69]. To the best of our knowledge, there are no specific animal models for MRC. A major challenge in animal model development is the narrow therapeutic window within the limited murine lifespan. In a recent study, two cell line models, UOK353 and UOK360, were derived from primary RMCs. Both cell lines exhibited loss of the *SMARCB1* gene and overexpression of several members of the polycomb repressive complex subunits, including EZH2, SUZ12, and EED. High-throughput drug screening of both cell lines indicated that they could be novel preclinical models for investigating the therapeutic approaches in MRC patients. Resultant data showed that combining cisplatin and bortezomib inhibited invasion and decreased cancer cell viability both *in vitro* and *in vivo* [70].

RMC is resistant to targeted mTOR inhibitors or anti-angiogenic therapies used in other subtypes of RCC, and only 29% of patients responded to cytotoxic chemotherapy in a multicenter retrospective study. Response to platinum-based therapy is short-lived, and the OS rate remains poor [71]. Given the highly invasive nature and poor outcomes of this disease, there is an urgent need to identify the molecular signature and therapeutic targets.

2. Main Therapeutic Approaches in Non-Clear Renal Cell Carcinoma (nccRCC)

Most studies have focused on studying ccRCC, and there are only limited studies focusing exclusively on nccRCC. In localized non-clear RCC, surgical practice is the most important and probably the only treatment approach. Metastatic non-clear RCCs are very challenging cancers to treat, and because there is no standard of care, there is disagreement amongst professionals regarding the best therapeutic option for these patients. Currently, cytokine therapy is not an effective treatment for nccRCC histology [72]. nccRCC patients are currently treated with tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs), and mTOR inhibitors. In the metastatic stages, the response and survival rates are lower than in ccRCC patients, and most nccRCC patients develop acquired drug resistance [73]. A schematic representation of major signaling pathways involved in the pathogenesis of nccRCC and therapeutic agents is shown in Figure 2. Exact understanding of the underlying signaling pathways of nccRCCs could improve the survival of these patients. Patients with advanced nccRCC might respond differently to pharmaceutical drugs, possibly because of differences in biological features of tumor subtypes. This demonstrates the importance of personalized medicine in the treatment of patients with RCC. Table 2 provides a summary of therapies targeting the major signaling pathways in nccRCC. In the following sections, we discuss major signaling pathways and clinical trial drugs in nccRCC patients.

Table 2. Therapies targeting the major signaling pathways in nccRCC.

Drug	Mechanism	Histologic Subtype	Therapeutic Effects of Drugs on nccRCC Patients	Survival Outcomes	Reference
Axitinib following progression on temsirolimus	TKI that targets VEGFRs, PDGFRs, and 2, and c-KIT	Papillary, chromophobe, *MiT* family translocation	Modest efficacy following progression on temsirolimus	Median PFS, ORR, median OS, and disease control rate were 7.4 months, 37.5%, 12.1 months, and 67.5%, respectively	[74]

Table 2. *Cont.*

Drug	Mechanism	Histologic Subtype	Therapeutic Effects of Drugs on nccRCC Patients	Survival Outcomes	Reference
Cabozantinib	Multi-target TKI that targets VEGFR2, c-MET, RET, Tyro3, Axl, and Mer	Papillary, chromophobe, *MiT* family translocation, and unclassified	Disease control in patients previously treated with VEGF-TKIs (savolitinib)	Median PFS, ORR, median OS, and disease control rate were 8.6 months, 14.3%, 25.4 months, and 78.6%, respectively	[75]
		Metastatic papillary, chromophobe, Xp11.2 translocation, unclassified, collecting duct carcinoma	Antitumor activity and safety	Median PFS, ORR, and median OS were 7.0 months, 27%, and 25.4 months, respectively	[76]
Pazopanib following progression on temsirolimus	Anti-VEGF TKI that targets VEGFRs, FGFR 1 PDGFRs, and 2, and c-KIT	Metastatic papillary, chromophobe, unclassified	Modest efficacy and safety, median PFS and OS	Median PFS and ORR were 16.5 months and 28%, respectively; median overall survival was not reached	[77]
Lenvatinib + everolimus	Multi-target TKI (targets VEGFRs, and FGFR) + mTORC1 inhibitor	Papillary, chromophobe, unclassified	Modest efficacy as first-line therapy; may be more effective in chromophobe RCC	Median PFS, ORR, and median OS were 9.23 months, 25.8%, and 15.64 months, respectively	[78,79]
Bevacizumab + everolimus	TKI + mTORC1 inhibitor	Papillary, chromophobe, RMC, unclassified RCC	Modest efficacy as an additional option. more effective in pRCC	Median PFS, ORR, and median OS were 13.7 months, 35%, and 33.9 months, respectively	[80]
Everolimus	mTORC1 inhibitor	Metastatic pRCC	Favorable median PFS and OS, and safety	Median PFS and median OS were 7.9–11.0 and 28.0–24.2 months, respectively	[81]
Temsirolimus	mTORC1 and mTORC2 inhibitor	Papillary, chromophobe	Improved PFS, OS, and stable disease rate	Median TTP, ORR, and median OS were 3.9 months, 5%, and 11.2 months, respectively	[82–85]

Abbreviations: FGFR: fibroblast growth factor receptor, mTOR: mammalian target of rapamycin, ORR: objective response rate, OS: overall survival, PD-1: programmed cell death 1, PDGFR: platelet-derived growth factor receptor, PFS: progression-free survival, pRCC: Papillary renal cell carcinoma, RMC: Renal medullary cell carcinoma, RCC: Renal cell carcinoma, TKIs: tyrosine kinase inhibitors, TTP: time to progression, VEGFR: vascular endothelial growth factor receptor.

2.1. Tyrosine Kinase Inhibitors (TKIs)

Tyrosine kinase receptors (TKRs), including c-MET, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), play important roles in various oncogenic cellular processes and progression of RCC. These receptors increase cell proliferation, survival, angiogenesis, and invasion of renal cancer cells. The expression of vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and their tyrosine kinase receptors is increased in RCC tumors. Therefore, administration of anti-TKR targeted therapy would be helpful for RCC treatment [86,87]. The results of clinical trials evaluating

the efficiency of TKI pharmaceutical agents in nccRCC are controversial. Some studies indicated that TKIs improved the response and survival rate in patients [74–77,88]. On the other hand, some studies demonstrated that these agents are not a good choice for the treatment of nccRCC patients [65,89–91]. Hence, further studies will lead to a better understanding of appropriate therapeutic approaches for nccRCC cases.

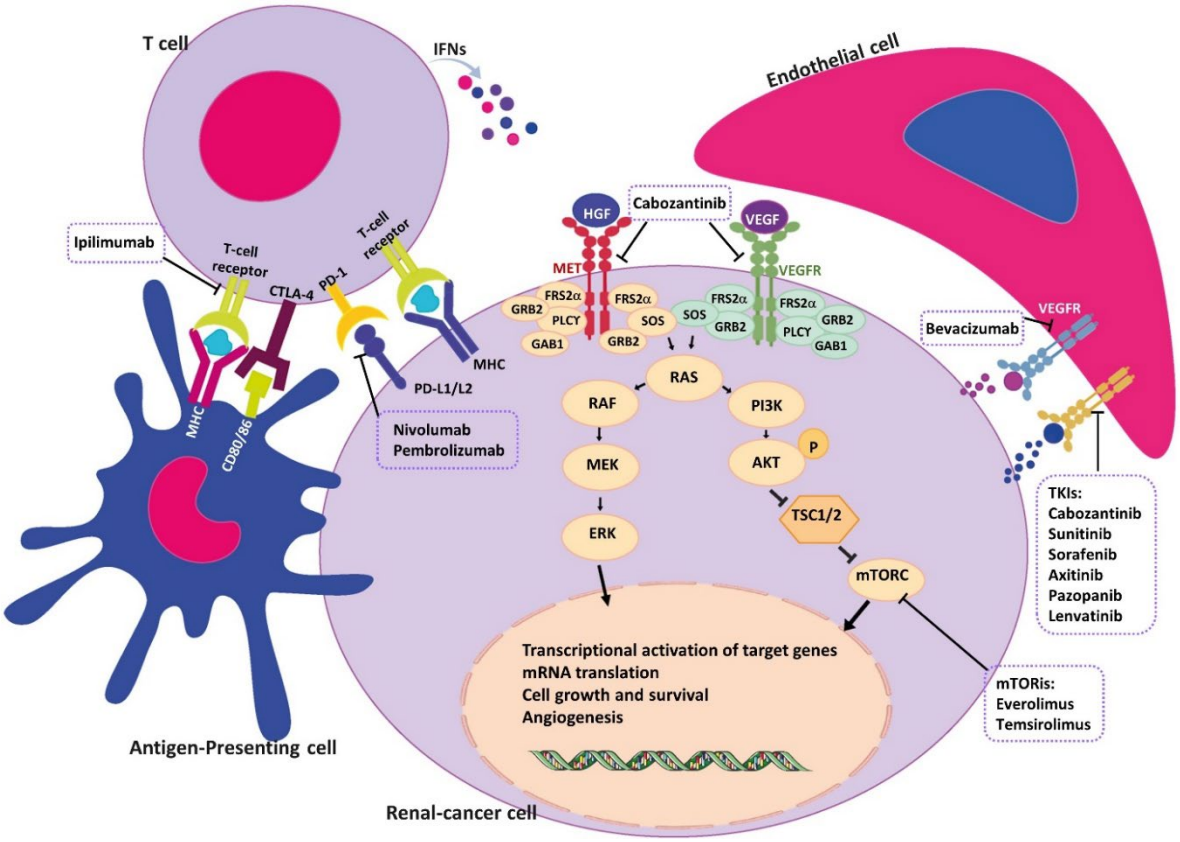

Figure 2. Schematic representation of major signaling pathways in the pathogenesis of nccRCC and therapeutic agents. VEGF and other involved growth factors secreted by renal cancer cells stimulate angiogenesis in the neighboring vascular endothelial cells. In renal cancer cells, growth factors (such as HGF and VEGF) binding to the TKRs (such as VEGFR and c-Met) induce several signaling cascades that lead to proliferation, invasion, survival, and angiogenesis in renal tumor cells. The increased activation of the mTOR pathway leads to the activation of cell growth, survival, metabolism, migration, and angiogenesis of tumor cells. Bidirectional cross-talk between endothelial and renal cancer cells leads to the progression of RCC. Antigen-presenting cells present tumor antigens to a naïve T cell, and after a set of cellular events, the T cell is activated. PD-1 is expressed on activated T cells and, upon binding to its ligand PD-L1/L2 on renal cancer cells, resulted in T cell exhaustion. This binding negatively regulates T cell activity and leads to evading the host immune system. Abbreviations: AKT: protein kinase B, ERK: extracellular signal-regulated kinase, FRS2a: fibroblast growth factor receptor substrate 2, GAB1: Grb2-associated binder 1, GRB2: growth factor receptor-bound protein 2, MAPK: mitogen-activated protein kinase, MEK: mitogen-activated protein kinase, P: phosphate group, MHC: major histocompatibility complex, PI3K: phosphatidylinositol 3-kinase, PD-1: programmed death-1, PD-L1: programmed death-ligand 1, PLC-γ: phospholipase C-γ, RAS/RAF: Rat sarcoma/rapidly accelerated fibrosarcoma, SOS: Son of Sevenless, VEGF: vascular endothelial growth factor.

A case study indicated that sorafenib improved progression-free survival with minimal side effects in a metastatic CDC patient [88]. Pazopanib and axitinib demonstrated tolerable safety and promising activity profiles in terms of objective response rate (ORR) and progression-free survival (PFS) in recurrent or metastatic nccRCC patients when used

after failure with other targeted therapy [74,77]. The efficacy and effectiveness of sunitinib, axitinib, and pazopanib are generally similar, but cabozantinib and sunitinib may produce better results than others. Campbell and colleagues indicated that cabozantinib improved OS and PFS in patients with advanced papillary, chromophobe, and translocation RCC subtypes. Furthermore, patients who had previously shown disease progression post-MET-targeted therapy (savolitinib before cabozantinib) achieved stable disease and improved PFS [75]. A multicenter and retrospective study showed that cabozantinib as first-line therapy versus sunitinib induced better safety and antitumor activity in metastatic nccRCC patients. CDC is often resistant to TKIs. However, this study indicated that cabozantinib could be efficient, at least in some CDC cases [76].

One study indicated that the treatment with multikinase inhibitors, including sorafenib, sunitinib, or axitinib, in metastatic papillary and chromophobe RCC has lower response rates than in ccRCC [89]. Many studies to date showed that CDC and RMC subtypes are resistant to TKI therapy. Several studies indicated that TKIs such as sorafenib and sunitinib have limited efficacy in the treatment of metastatic CDC [90,91]. These events may result from intrinsic and acquired resistance mechanisms. One hypothesis has proposed that the combinations of anti-cancer drugs could have beneficial effects in treating these subtypes of RCC. *In vitro* and *in vivo* preclinical models could be used to investigate potential drugs, improve understanding of resistance mechanisms, and discover potential therapeutic targets. We will overview several studies that combine two or more TKIs with mTOR inhibitors in treating nccRCC subtypes.

2.2. Mammalian Target of Rapamycin Inhibitors (mTORis)

The phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway controls nucleotide and protein synthesis, translation, glucose/lipid metabolism, cell survival, and proliferation and thereby has a crucial role in cell growth, differentiation, survival, metabolism, migration, and angiogenesis of tumor cells. This signaling pathway is stimulated by various paracrine and autocrine factors such as hormones, cytokines, growth factors, and several environmental signals. Dysregulation of this signaling pathway was reported in different types of RCC and is related to metastasis and lower survival rate. Therefore, pharmacological inhibitors of the PI3K/AKT/mTOR signaling cascade are promising drug candidates for RCC [92].

Although the efficacy of mTORC1 inhibitors (such as temsirolimus, sirolimus, and everolimus) has predominantly been developed in ccRCC, further analysis of temsirolimus (25 mg intravenously weekly) suggested this mTOR1 inhibitor has more median overall and PFS compared with interferon in nccRCC patients, 75% of which were of the papillary subtype [82]. Other studies confirmed that temsirolimus improved the survival and duration of stable disease and was associated with a better quality of life in nccRCC patients [83–85,93,94]. A randomized phase II trial showed that patients with metastatic nccRCC may have a lower tumor control rate and shorter PFS when treated with temsirolimus compared to sunitinib [95].

Everolimus (an mTOR serine/threonine kinase inhibitor) provides clinical benefit to patients with nccRCC, offering promising OS results and a tolerable side-effect profile [81,96]. A phase II trial in European patients with metastatic papillary RCC (RAD001 in Advanced Papillary Tumor Program in Europe (RAPTOR) trial; NCT00688753) indicated that oral everolimus (10 mg daily) monotherapy could be considered a therapeutic approach to achieve safety and a favorable median PFS and OS [81]. Many studies indicated that combining mTOR inhibitors with non-mTOR-based therapies could maximize efficacy and tolerability [80,97]. A phase II clinical trial proved that the combination of everolimus and the anti-VEGF monoclonal antibody bevacizumab is an effective therapy with good tolerability for patients with metastatic papillary variant nccRCC [80]. A case study of a patient with metastatic pRCC showed that the combination of lenvatinib (a multitargeted tyrosine kinase inhibitor) and everolimus was useful for more than 2 years [97]. A multicenter phase II trial investigated the efficacy and tolerability of the combination of lenvatinib

(18 mg once daily) and everolimus (5 mg once daily) in advanced nccRCC (papillary and chromophobe) patients following one prior antiangiogenic therapy. The data indicated that a combination of lenvatinib and everolimus has hopeful antitumor activity as first-line therapy in these patients. This clinical trial demonstrated that the survival rate improved with increasing tumor ORR (25.8%) compared to the everolimus monotherapy [78,79]. Another study investigated the efficacy of the combination of lenvatinib and everolimus in metastatic RCC after progression on immune checkpoint inhibitors (ICIs) and VEGFR-TKIs (cabozantinib, sunitinib, and pazopanib). These treatments demonstrated meaningful clinical activity with improved PFS, ORR, and OS in patients with advanced RCC [98].

Unfortunately, disruption of several major signaling pathways leads to intrinsic and acquired resistance to mTOR inhibitors. Preclinical studies indicated that continuous activation of RPS6KB1, stimulation of glycogen synthase kinase 3β (GSK3β)–EIF4EBP1 and PI3K/AKT/MAPK signaling pathways, deregulation of apoptosis (Decreased BCL2 Associated X, Apoptosis Regulator (BAX) expression, and BCL2 Apoptosis Regulator (BCL-2) upregulation), and promotion of epithelial-to-mesenchymal transition (EMT) are the major mechanisms of resistance to the administration of mTOR inhibitors [2].

2.3. Immune Checkpoint Inhibitors (ICIs)

ICIs have therapeutic effects in advanced ccRCC and have become standard treatment options in this setting. There are only limited studies supporting the effectiveness of ICIs in nccRCC patients. Programmed death ligand-1 (PD-L1) expression in these tumors is related to higher tumor stage and worse clinical outcomes [99]. It is predicted that any nccRCC subtype responds differently to ICIs since they have a specific tumor immune microenvironment. ICI therapies result in T cell-mediated tumor cell death following the activation of immune pathways. As a result, T cell-inflamed tumors, which show evidence of high infiltration of tumor-reactive T cells (such as cytotoxic T lymphocytes), are more likely to respond to ICIs than non-T cell-inflamed tumors [100]. The binding of two cell surface receptors of immune cells, programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4), to their ligands on tumor cells results in inhibiting the cellular immune response. These mechanisms lead to tumor-mediated immune suppression [101,102]. Therefore, the ICIs targeting PD-1/PD-L1 (nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) are approved to treat RCCs [103].

Some studies have evaluated the ICI therapeutic potential for nccRCC tumors following reports on clinical success in ccRCC [102]. In a multicenter analysis, the modest anti-tumor activity of PD-1/PD-L1 inhibitors was observed in a heterogeneous population of patients with nccRCC. In this 43-patient cohort study, 29% of patients with papillary RCC histology objectively responded, and the median OS was 12.9 months [101]. In a single-institution retrospective study, the safety of nivolumab treatment was assessed in patients with non-clear cell kidney cancer. In this study, different responses were demonstrated in various nccRCC histologies. The highest response rate was in patients with unclassified histology, while no responses were observed in chromophobe and papillary type 2 patients [104]. Furthermore, a multicenter retrospective study reported the efficacy of nivolumab monotherapy in a cohort of 41 patients with nccRCC and an objective response rate of 20%. In this analysis, the anti-tumor activity of nivolumab was seen in papillary, unclassified, and collecting duct non-clear cell histologies, suggesting the use of nivolumab in the treatment of patients with nccRCC [105]. The combination of ICI activities was also assessed in a multicenter retrospective analysis, in which the ipilimumab plus nivolumab (CTLA 4 + PD-1) treated nccRCC cohort showed a median PFS of 7.1 months and ORR of 33 [106]. In a phase II trial study of pembrolizumab monotherapy, including 165 patients with advanced nccRCC (Keynote 427 cohort B), the ORR of all patients and 118 papillary RCCs were 24.8% and 25.4%, respectively. Based on the findings, the anti-tumor activity of pembro was shown in nccRCC, more specifically in papillary tumor type [93]. Another trial (phase IIIb/IV) was designed to investigate the efficacy of nivolumab monotherapy in

patients with advanced nccRCC, which demonstrated that 240 mg flat dose of this blocker every 2 weeks (Q2W) could be a treatment option in nccRCC patients [107].

Since these studies evaluated the ICI treatment for all nccRCC subtypes, other groups focused specifically on one non-clear cell histology. De Vries-Brilland et al. reported the clinical activity of PD-1/PD-L1 blockades in metastatic papillary RCC with an ORR of 26.1% and a median OS of 14.6 months [108]. There are some case reports of patients with chromophobe renal cell carcinoma treated with nivolumab. In one of the case reports, Rouvinov and colleagues exhibited a remarkable response to nivolumab as a second-line treatment. In this study, the patient with advanced chRCC received nivolumab 3 mg/kg every 2 weeks. A partial response was noted after six cycles, supporting the fact that immunotherapy could be a therapeutic approach in patients with chromophobe histology after first-line therapy failure [109]. In another case report, a 41-year-old woman received nivolumab as a seventh-line treatment for four cycles and showed clinical improvements with no significant side effects. As a result, she continues with this treatment [110]. However, in one study, metastatic chRCC patients treated with nivolumab showed no objective responses, which was hypothesized to be related to the low PD-L1 expression [111]. Regarding the RMC subtype, Sodji et al. reported different clinical outcomes of nivolumab treatment in two cases. They demonstrated responses and a short period of disease stabilization only in patient 1, while patient 2 had disease progression and showed no response [112]. The clinical activity of anti-PD-1 based therapies was also reported in another RMC case report study [113]. Based on these studies, checkpoint inhibitors could be a novel therapeutic approach for advanced nccRCC, in which the therapeutic options are very limited. Table 3 summarizes therapies with ICIs in nccRCC.

Table 3. Therapies with immune checkpoint inhibitor (ICI) pathways in non-clear cell renal cell carcinoma (nccRCC).

Drug	Mechanism	Histologic Subtype	Therapeutic Effects of Drugs on nccRCC Patients	Reference
PD-1/PD-L1 blockade monotherapy	PD-1/PD-L1 pathway	Papillary, chromophobe, unclassified, translocation	Modest anti-tumor activity	[101]
		Type 1 pRCC, type 2 pRCC and unclassified pRCC.	Limited activity in papillary tumor type and disease progression in 53% of patients	[108]
Nivolumab	PD-1/PD-L1 pathway	Papillary, unclassified, chromophobe, translocation mucinous tubular and spindle cell carcinoma	Clinical activity in unclassified nccRCC with no responses in chromophobe and papillary type 2 patients	[104]
		Papillary, unclassified, chromophobe, collecting duct, Xp11 translocation and mucinous tubular and spindle cell carcinoma	Anti-tumor activity of nivolumab in papillary, unclassified, and collecting duct histologies	[105]
		Papillary, chromophobe, unclassified, other	Safety and improved ORR, median PFS and median OS	[107]
		Chromophobe	Modest activity as a second line treatment with partial response	[109]

Table 3. *Cont.*

Drug	Mechanism	Histologic Subtype	Therapeutic Effects of Drugs on nccRCC Patients	Reference
Nivolumab		Metastatic chromophobe	Clinical improvements with no significant side effects	[110]
		Metastatic chromophobe	No objective responses	[111]
		Metastatic renal medullary carcinoma	Responses only in patient 1 followed by progression after 15 months	[112]
		Renal medullary carcinoma	Complete response for more than 9 months.	[113]
Pembrolizumab	PD-1/PD-L1 pathway	Papillary, chromophobe, unclassified	Safety and anti-tumor activity in nccRCC, more efficient in papillary subtype and unclassified	[93]
Ipilimumab + nivolumab	PD-1/PD-L1 pathway + CTLA-4	Papillary, chromophobe, unclassified adenocarcinoma translocation medullary	Favorable ORR and median PFS	[106]

Abbreviations: CTLA-4: cytotoxic T-lymphocyte-associated protein 4, nccRCC: non-clear cell renal cell carcinoma, ORR: objective response rate, OS: overall survival, PD-1: programmed cell death protein-1, PD-L1: programmed death ligand-1, PFS: progression-free survival, pRCC: papillary renal cell carcinoma.

2.4. Chemotherapy

Cytotoxic chemotherapy is the mainstay of medical treatment in collecting duct carcinoma and renal medullary carcinoma, which are generally resistant to other systemic therapy options [65,114]. To support the clinical potential of this treatment, in a prospective study investigating the efficacy of platinum-based chemotherapy in patients with metastatic collecting duct carcinoma, the ORR, median PFS, and OS were 26%, 7.1, and 10.5 months, respectively [114]. In contrast, another study showed that only 13% of patients with RMC survived for more than 2 years following chemotherapy. Based on these results, there is an urgent need to provide more effective treatment for RMC patients [115].

3. Conclusions

Therapeutic options for nccRCCs are limited, and these RCC subtypes are treated in the same way as the more common ccRCC. Furthermore, most clinical research concentrates on ccRCC. The prognosis and efficacy of therapeutic approaches are the key challenges for future research on nccRCC subtypes. Establishing appropriate *in vitro* and *in vivo* models recapitulating distinct subtypes of nccRCCs may lead to a better understanding of their pathophysiology and the development of novel anti-tumor targeted therapies that will revolutionize cancer treatment in the future.

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Abbreviations

2D: two-dimensional, 3D: three-dimensional, AKT: protein kinase B, BHD: Birt-Hogg-Dube, ccRCC: clear-cell RCC, CDX: cell line-derived xenograft, chRCC: chromophobe RCC, DOX: doxycycline, CTLs: cytotoxic T lymphocytes, CTLA-4: cytotoxic T-lymphocyte-associated protein 4, FGFR: fibroblast growth factor receptor, FLCN: frameshift or nonsense mutations of tumor-suppressor folliculin, GEM: genetically engineered mouse models, HGF: hepatocyte growth factor, hiPSCs: human inducible pluripotent stem cells, ICI: immune checkpoint inhibitors, MET: mesenchymal to epithelial transition [hepatocyte growth factor receptor], mTOR: mammalian target of rapamycin, mTORis: mammalian target of rapamycin inhibitors, nccRCC: non-clear cell renal cell carcinoma, ORR: objective response rate, OS: overall survival, PD-1: programmed cell death protein-1, PD-L1: programmed death ligand-1, PDGFR: platelet-derived growth factor receptor, PDX: patient-derived xenografts, PFS: progression-free survival, PI3K: phosphoinositide 3-kinase, pRCC: papillary renal cell carcinoma, RMC: renal medullary cell carcinoma, RCC: renal cell carcinoma, VHL: von Hippel–Lindau, TKIs: tyrosine kinase inhibitors, TKR: tyrosine kinase receptor, VEGF: vascular endothelial cell growth factor, VEGFR: vascular endothelial growth factor receptor.

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