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Review

Genomic profiling and molecular characterization of non-clear cell renal cell carcinoma: a narrative review from a clinical perspective

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Abstract: While the clear-cell renal cell carcinoma (ccRCC) treatment has undergone several paradigm shifts in recent years, the non-clear cell renal cell carcinoma (nccRCC) therapeutic approach has yet to be extensively investigated and improved. The WHO 2022 classification of renal neoplasms redefined the most common nccRCC subtypes (papillary and chromophobe RCC) and introduced the molecularly defined RCC class, which is a first step in the direction of better molecular profiling of nccRCC. We reviewed the literature data on known genomic alterations of clinical interest in nccRCC and discussed their potential role in guiding therapeutic choices in each nccRCC entity. Among the alterations discussed, we focused on the ones that could be treated with already available drugs, such as MET (N-methyl-N′-nitro-N-nitrosoguanidine)-driven papillary RCC, mechanistic target of rapamycin altered chromophobe RCC, anaplastic lymphoma kinase-rearranged RCC, and fumarate-hydratase deficient RCC. Furthermore, we focused on the currently ongoing clinical trials and further evidence for all the other entities, such as SMARCB1-deficient RCC, TFE3 and transcription factor EB (TFEB)-altered RCC, and Elongin C (ELOC)-mutated RCC. The vast heterogeneity of nccRCC does not allow a one-size-fits-all solution; therefore, molecular characterization is the path toward effective therapies and fully personalized medicine for these entities.

Keywords: agnostic therapy, chromophobe RCC, Genomic Profiling, MET, molecularly defined RCC, mTOR, non-clear renal cell carcinoma, papillary RCC

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Introduction

Renal cell carcinoma (RCC) is the most common renal neoplasm.[1] The clear cell histotype (ccRCC) is the most frequent, representing two-thirds of the whole population, while the other cases are grouped as non-clear cell RCC (nccRCC), an umbrella definition, that includes many different histologies.

The median overall survival for metastatic ccRCC has greatly increased from less than 1 year in the 1990s to more than 4 years in some recently concluded trials.[2] Major paradigm shifts have been observed: starting from the rudimentary cytokine-based immunotherapies (high-dose interleukin 2 and interferon-α) with poor outcomes, the systemic treatment of metastatic ccRCC evolved with the introduction of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI), mechanistic target of rapamycin inhibitors (mTORi), and immune checkpoint inhibitors (ICI). More recently, based on robust randomized phase III data, VEGFR-TKI/ICI combinations have gained the role of first-line therapeutic standard of care for ccRCC. Finally, a novel small-molecule inhibitor of

hypoxia-inducible factor 2α (HIF2a-inhibitor), belzutifan, has recently been added to the therapeutic armamentarium for advanced ccRCC.[3]

For the nccRCCs, the issue is trickier because although it is a histologically and molecularly heterogeneous group, most trials were not targeted at specific nccRCC histotypes, and favorable efficacy results were only achieved in a limited number of patients. For the management of metastatic nccRCC, NCCN Guidelines[4] recommend cabozantinib and sunitinib monotherapy as preferred first-line treatments (category 2A) based on the results of the phase II SWOG 1500 trial[5] and the two randomized phase II trials ASPEN[6] and ESPN,[7] respectively; instead recommend ICI monotherapy, ICI plus VEGFR-TKI or everolimus plus lenvatinib as alternative therapeutic options. ESMO Guidelines[8] suggest, as preferred options in the first-line setting, cabozantinib monotherapy [II, B] and, as alternative treatment options sunitinib [II, B] or pembrolizumab [III, B] monotherapy. Combination therapies have also shown an efficacy benefit for metastatic nccRCC, but to a much smaller magnitude than for ccRCC. Specifically, the combination of two ICI, nivolumab and ipilimumab, yielded positive results in the HCRN GU16-260 phase II trial[9] and the Checkmate 920 phase IIIb/IV trial,[10] and the combination of nivolumab and cabozantinib was proven safe and effective in a single-arm phase II trial.[11,12] More recently, a phase II single-arm prospective trial (KEYNOTE-B61) proved the efficacy of a VEGFR-TKI plus ICI combination, lenvatinib plus pembrolizumab, in nccRCC patients.[13] The reported efficacy was the highest among all prospective studies including nccRCC patients, but it was underwhelming if compared to the performance of the same combination in the ccRCC patients.[14] In addition, there is no standardized second-line treatment, with little real-world evidence on VEGFR-TKI monotherapy and everolimus monotherapy.[15–17] An overview of the major clinical trials enrolling patients with nccRCC, regardless of the specific subtype, is presented in Table 1.

A more efficient approach to nccRCC therapeutic management could result from genomic profiling of different nccRCC histologies, which is also advocated for ccRCC.[35] Given the heterogeneous nature of this group, it is unlikely to provide a one-size-fits-all strategy. The tendency toward a profiling-based approach can be already seen in the most recent classification of urogenital tumors,[36] which identifies a total of 21 different forms of RCC, including a new category called "molecularly defined RCC." This category includes TFE3-rearranged RCC, TFEB-rearranged, and TFEB-amplified RCC, Fumarate Hydratase (FH)-deficient RCC, succinate dehydrogenase (SDH)-deficient RCC, anaplastic lymphoma kinase (ALK)-rearranged RCC, ELOC (formerly TCEB1)-mutated RCC, and SMARCB1 (INI1)-deficient RCC.[36,37] The molecular data underpinning these entities seem to be relevant in the differential diagnosis from a pathological point of view; however, their predictive value is still to be defined properly.[38]

Since nccRCC suffers from a general lack of prospective data-supported treatments and its therapeutical management is borrowed from the experience with ccRCC, a major therapeutic shift is needed to properly address these histotypes. The knowledge of molecular data and the design of molecularly informed therapeutic strategies could be the breakthroughs required in nccRCC clinical management.

The present paper aims to review the most recent literature to depict a clear landscape of mutational signatures in nccRCC, highlighting the possibility of clinical exploitation.

Molecular alterations of clinical interest in the principal non-clear cell RCC

Papillary RCC

Papillary RCC (pRCC) accounts for 10%–20% of all RCC cases and represents the most frequent nccRCC.[39] Before WHO 2022 classification, pRCC was distinguished into type 1 and type 2 on a morphologic basis. Although this distinction has been used by clinicians as a helpful prognostic tool, the WHO 2022 classification eliminated this division, mainly for two reasons: the fact that mixed tumor phenotypes are very common and the realization that many tumors that fall into the pRCC type 2 category had a substantially different molecular background.[40] Moreover, a wide analysis of available data demonstrated that this dichotomous categorization does not influence patient outcomes when adjusting for disease stage and other classic prognostic features.[41]

The first studied oncogene for pRCC was MET (also known as hepatocyte growth factor receptor). Activating mutations of MET were

Table 1. Major clinical trials designed for all nccRCC histotypes.

Trial name	Phase	Patients	Study arms	Outcomes
Completed trials				
NCT01219751[18]	II	31 advanced nccRCC-naïve patients	Single arm: sunitinib	ORR: 35%, CR: 0%, mPFS 6.4 mts, mOS: NR (estimated 25.6 mts)
NCT01108445 "ASPEN"[6]	II	108 advanced nccRCC-naïve patients	Randomized: sunitinib vs everolimus	ORR: 18% vs 9%, CR: 0% vs 4%, mPFS 6.1 mts vs 4.1 mts, mOS: 16.2 mts vs 14.9 mts
NCT01185366 "ESPN"[7]	II	70 advanced nccRCC-naïve patients	Randomized: sunitinib vs everolimus	ORR: 9% vs 3%, CR: 0% vs 0%, mPFS 8.3 mts vs 5.6 mts, mOS: 31.5 mts vs 13.2 mts
NCT00979966 "CESAR"[19]	IIa	22 advanced nccRCC-naïve patients	Randomized: sunitinib vs temsirolimus	ORR: 3% vs 2%, CR: 0% vs 0%, mPFS 13.2 mts vs 9.3 mts, mOS: 19.8 mts vs 19.4 mts
NCT01538238[20]	II	29 advanced nccRCC-naïve patients	Single arm: pazopanib	ORR: 29%, CR: 0%, mPFS 16.5 mts, mOS: NR
NCT01798446[21]	II	40 advanced nccRCC patients in progression after temsirolimus	Single arm: axitinib	ORR: 37.5%, CR: 0%, mPFS 7.4 mts, mOS: 12.1 mts
NCT01399918[22]	II	37 advanced nccRCC-naïve patients	Single arm: everolimus + bevacizumab	ORR: 35%, CR: 0%, mPFS 13.7 mts, mOS: 35.9 mts
NCT02915783[23]	II	31 advanced nccRCC-naïve patients	Single arm: everolimus + lenvatinib	ORR: 26%, CR: 0%, mPFS 9.2 mts, mOS: 15.6 mts
NCT02596035 "CheckMate-374"[24]	IIIb/IV	44 advanced nccRCC-naïve or pretreated (⩽1 line) patients	Single arm: nivolumab	ORR: 13.6%, CR: 2.3% mPFS 2.2 mts, mOS: 16.3 mts
NCT02853344 "KEYNOTE-427 cohort B"[25]	II	165 advanced nccRCC-naïve patients	Single arm: pembrolizumab	ORR: 26.7%, CR: 6.7%, mPFS: 4.2 mts, mOS: 28.9 mts
NCT02724878[26]	II	42 advanced nccRCC-naïve or pretreated (⩽1 line) patients	Single arm: atezolizumab + bevacizumab	ORR: 26%, CR: 0%, mPFS: 8.3 mts, mOS: NR
NCT03170960[27]	Ib/II	32 advanced nccRCC-naïve or pretreated (⩽1 line) patients	Single arm: atezolizumab + cabozantinib	ORR: 31%, CR: 0%, mPFS: 9.5 mts, mOS: NR
NCT03117309 "HCRN GU16-260-Cohort B"[9]	II	35 advanced nccRCC-naïve patients	Single arm: nivolumab → nivolumab + ipilimumab	ORR : 14.3%, CR: 5.7%, mPFS: 4.0 mts, mOS: NR
NCT02982954 "ChekMate-920"[10]	IIIb/IV	52 advanced nccRCC-naïve patients	Single arm: nivolumab + ipilimumab	ORR: 19.6%, CR: 4.3%, mPFS: 3.7 mts, mOS: 21.2 mts
NCT03635892 "CA209-9KU"[11,12]	II	47 advanced nccRCC-naïve or pretreated (⩽1 line) patients	Single arm: nivolumab + cabozantinib	ORR: 48%, CR: 4%, mPFS: 12.5 mts, mOS: 28.0 mts
NCT04704219 "KEYNOTE-B61"[13]	II	158 advanced nccRCC-naïve patients	Single arm: pembrolizumab + lenvatinib	ORR: 49%, CR: 6%, mPFS: 18 mts, mOS: NR
NCT05220267[29]	II	43 advanced nccRCC-naïve patients	Single arm: anlotinib + sintilimab	ORR: 52.9%, mPFS: 15.1 mts, mOS: NR

(Continued)

Table 1. (Continued)

Trial name	Phase	Patients	Study arms	Outcomes
NCT03075423 "SUNNIFORECAST"[30]	II	309 advanced nccRCC-naïve patients	Randomized: nivolumab + ipilimumab vs standard of care	ORR: 32.8% vs 19.6%, mPFS: 5.52 mts vs 5.65 mts, mOS: 42.4 mts vs 33.9 mts
Ongoing trials				
NCT03866382[28]	II	224 advanced rare genitourinary cancer-naïve or pretreated (⩽2 line) patients	Single arm: nivolumab + ipilimumab + cabozantinib	Estimated completion: 2025
NCT04413123[31]	II	60 advanced nccRCC-naïve or pretreated (⩽1 line) patients	Single arm: nivolumab + ipilimumab + cabozantinib	Estimated completion: 2025
NCT04267120 "LENKYN trial"[32]	II	34 advanced nccRCC-naïve patients	Single arm: pembrolizumab + lenvatinib	Estimated completion: 2027
NCT05678673 "STELLAR-304"[33]	III	291 advanced nccRCC-naïve patients	Zanzalintinib + nivolumab vs sunitinib	Estimated completion: 2028
NCT03595124 "AREN1721"[34]	II	40 advanced translocation RCC-naïve or pretreated (⩽1 line) patients	Randomized: nivolumab + axitinib vs nivolumab	Estimated completion: 2031

Data were acquired from clinicaltrial.gov (accessed on September 22nd, 2024).
CR, complete response; mts, months, mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate.

originally identified in hereditary pRCC cases,[42] and subsequently in many sporadic cases.[43] MET is involved in cell motility, growth, and survival,[44] and, as a consequence, dysregulation of its activity can lead to apoptosis resistance, angiogenesis boosting, and cell invasion.[45] Many types of mechanisms can lead to these effects: increased copy number of chromosome 7, alterations with the MET gene, and transcriptional upregulation of MET. Overall MET upregulation is described in over 80% of pRCC.[43] Given the centrality of this oncogene, MET alterations could have a predictive role in MET-targeting therapies. However, specific MET-targeting drugs reported poor results in pRCC: tivantinib, a c-MET-inhibitor, phase II trial was stopped due to futility,[46] while crizotinib, an ALK-inhibitor, and savolitinib, a c-MET-inhibitor, monotherapies were inferior to cabozantinib (a multi-kinase inhibitor, which also targets MET) in the PAPMET phase II trial.[5] The only positive results come from the phase II trial of foretinib, a c-MET and VEGFR inhibitor, which showed a Disease Control Rate (DCR) of nearly 100% in the MET-mutated patients (both germinal and somatic mutations), but with a dismal Progression-Free Survival (PFS) of 9.3 months.[47] Better results come from a single-arm phase II trial (CALYPSO) evaluating the efficacy of the ICI durvalumab plus savolitinib in all pRCC patients regardless of MET status.[48] While the study was overall negative for reporting an ORR of 29% and a median PFS of 4.9 months in the intention to treat population, the MET-driven population reported an ORR of 53% and a median PFS of 12 months. Another similar experimentation is going on with specific savolitinib in combination with ICI in MET-altered pRCC, the SAMETA phase III trial (savolitinib + durvalumab vs sunitinib + durvalumab) whose results are expected for 2024 (NCT05043090). Hopefully, the growing body of evidence on MET-driven pRCC will help to understand the effective predictive potential of MET alterations.

Among other mutations of potential clinical interest, pRCC displays some mutations also observed in ccRCC,[35] albeit less frequently. CDKN2A and CDKN2B deletion or hypermethylation are described in many pRCC cases, mostly in those formerly classified as type 1 pRCC, whereas mutations in chromatin regulators, such as PBRM1, BAP1, and SETD2, are less frequent and mostly happen in those cases formerly classified as type 2 pRCC.[43,49]

Another relatively common pRCC mutation of potential clinical interest is the mutation of the TERT (TElomerase Reverse Transcriptase)

promoter. Mutations of this gene are found across many types of cancers, the most frequent being bladder cancer, melanoma, thyroid cancer, glyoma, and head and neck cancer.[50] which correlates with larger tumors, metastatic development, and reduced overall survival.[39] At present, TERT promoter mutation is not therapeutically exploitable, but favorable preclinical evidence exists for TERT inhibitor.[51]

An overview of the major clinical trials enrolling pRCC patients is presented in Table 2.

Table 2. Major clinical trials designed for pRCC histotype.

Trial name	Phase	Patients	Study arms	Outcomes
Completed trials				
NCT00541008 SUPAP[52]	II	62 advanced pRCC-naïve patients	Single arm: sunitinib	ORR 12%; CR 0%; mPFS 15 mts; mOS 15.1 mts
NCT02127710[53]	II	111 advanced pRCC pretreated (⩽1 line) patients	Single arm: savolitinib monotherapy	ORR 18%, CR 0% (MET driven) and ORR 0%, CR 0% (non-MET driven); mPFS 6.2 mts (MET driven) and 1.4 mts (non-MET driven)
NCT02019693[54]	II	20 advanced pRCC pretreated (⩽3 line) patients	Single arm: capmatinib monotherapy	ORR 15%; CR 0%; mPFS 10.2 mts; mOS 31 mts
NCT00060307 SWOG S0317[55]	II	45 advanced pRCC naïve-patients	Single arm: erlotinib	ORR 11%; CR 0%; 4 mts-PFS 44%; mOS 27 mts
NCT01688973[46]	II	55 advanced pRCC pretreated (⩽1 line) patients	Tivantinib vs tivantinib + erlotinib	ORR 0% and CR 0% in both arms; mPFS 2 mts vs 3.9 mts
NCT00726323[47]	II	72 advanced pRCC pretreated patients	Single arm: foretinib monotherapy	ORR 13.5%; CR 0%; mPFS 9.3 mts; mOS NR; MET is a predictive factor for response
NCT03091192 "SAVOIR"[56]	III	60 advanced pRCC MET-driven naïve-patients	Randomized: savolitinib vs sunitnib	ORR 27% vs 7%; CR 0% vs 0%; mPFS 7.0 mts vs 5.6 mts; mOS NR mts vs 13.2 mts
NCT01524926 "CREATE"[57]	II	23 advanced pRCC naïve-patients	Single arm: crizotinib	ORR 50%, CR 0% (MET driven) and 6.3%, CR 0% (non-MET driven); 1-year PFS 75% (MET driven) and 27.3% (non-MET driven); 1-year OS 75% (MET driven) and 71.8% (non-MET driven)
NCT02761057 "PAPMET"[5]	II	152 advanced pRCC pretreated (⩽1 line) patients	Randomized: sunitinib vs cabozantinib vs crizotinib vs savolitinib	ORR 4% vs 23% vs 0% vs 3%; CR 0% vs 5% vs 0% vs 0%; mPFS 5.6 mts vs 9.0 mts vs 2.8 mts vs 3.0 mts; mOS 16.4 mts vs 20.0 mts vs 19.9 mts vs 16.4 mts
NCT02819596 "CALYPSO"[48]	II	41 advanced pRCC naïve- or pretreated (⩽1 line) patients	Single arm: durvalumab + savolitinib	CR 29% (53% in MET driven); mPFS 4 mts (12 mts in MET driven); mOS 14.1 mts (27.4 mts in MET driven)
Ongoing trials				
NCT05043090 "SAMETA"[58]	III	220 advanced pRCC MET-driven naïve-patients	Randomized: durvalumab + savolitinib vs durvalumab vs savolitinib	Estimated completion: 2026

Data were acquired from clinicaltrial.gov (accessed on September 22nd, 2024).
CR, complete response; mts, months; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate.

Chromophobe RCC

Chromophobe renal cell carcinoma (chRCC) represents 5% of all RCC cases.[59] It is a disease with an overall better course than those of other RCCs (5-year OS over 80%).[60] The few cohorts with genomic analyses offer a picture of chRCC as a tumor with low mutation frequency. Among the most frequently mutated genes are the tumor suppressors TP53 and PTEN.[61] Both mutations are also correlated with worse overall survival and are more frequent in metastatic diseases.[62] Another frequent mutation is the rearrangement of the TERT promoter, which is considered to be a pivotal driver in chRCC.[61,63] However, none of these mutations is clinically exploitable.

Another key aspect of chRCC is metabolic rewiring: many chRCC display mutations of the Krebs cycle enzymes or the electron transport chain. Moreover, 23% of the cases present alterations of mTOR and/or its downstream, and these mutations are pejorative of the prognosis.[63,64] In chRCC, mTOR activating mutations are pivotal in the aforementioned metabolic rewiring. Moreover, these mutations act by redirecting autophagy processes toward energy production. Although mTOR inhibitors showed some efficacy in chRCC, clear evidence for mTOR mutations to predict mTORi response in chRCC remains still debated. The major clinical trials enrolling, among others, patients with chRCC are reported in Table 1.

Collecting duct RCC

Collecting duct carcinoma (cdRCC) or Bellini duct carcinoma is a rare type of RCC that probably originates from renal collecting duct epithelium.[65] While it was originally described as a close relative of upper tract urothelial carcinoma (UTUC), this idea has been recently challenged. In fact, cdRCC has some characteristic gains at 13q and losses at 1p, 8p, 9p, and 16p, which UTUC completely lacks.[66] Moreover, a gene expression profiling analysis proved that the cdRCC transcriptome is far closer to normal kidney tissue than UTUC.[67] Thanks to recent advances in molecular and immunohistochemical tools, recent studies have reclassified a significant proportion of previously diagnosed collecting duct carcinomas as FH-deficient and SMARCB1-deficient RCCs.[68–69]

As for the DNA mutations in this neoplasm, the DNA repair gene NF2 (14%), the tumor-suppressor FBXW7 (8%), and CDKN2A (8%) are the most represented.[64] Collecting duct RCC is known for its relatively low mutation burden (1.8 Mutations/Mb) and its strong tendency toward microsatellite stability.[70]

The main oncologic treatment proposed for cdRCC has been platinum-based chemotherapy, due to its similarity with UTUC.[71,72] However, the multi-kinase inhibitor cabozantinib has recently shown efficacy in a phase II clinical trial [35420628].[73]

An overview of the major clinical trials enrolling cdRCC patients is presented in Table 3.

Molecular alterations of clinical interest in molecularly defined RCC

The latest WHO 2022 classification describes specific molecular alterations that characterize small subgroups of tumors such as TFE3-rearranged RCC, TFEB-rearranged, and TFEB-amplified

Table 3. Major clinical trials are designed for cdRCC patients only.

Trial name	Phase	Patients	Study arms	Outcomes
Completed trials				
Oudard et al.[71]	II	23 cdRCC naïve-patients	Single arm: gemcitabin + cisplatin or carboplatin	ORR: 26%; CR 4%; mPFS: 7.1 mts; mOS: 10.5 mts
Rizzo et al.[72]	Retrospective	35 cdRCC naïve-patients	Platinum-based chemotherapy	ORR: 22.2%; CR 0%; mPFS: 6 mts; mOS: 8 mts
NCT03354884 "BONSAI"[73]	II	23 cdRCC naïve-patients	Single arm: cabozantinib	ORR: 35%; CR 4%; mPFS: 4 mts; mOS: 7 mts

Data are acquired from clinicaltrial.gov (accessed on September 22nd, 2024).
CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate.

RCC, FH-deficient RCC, SDH-deficient RCC, ALK-rearranged RCC, ELOC (formerly TCEB1)-mutated RCC, and SMARCB1 (INI1)-deficient RCC. The clinical interest of these mutations is however difficult to define since these subtypes are often rare and not included in most prospective clinical trials.

TFE3-rearranged RCC

TFE3 rearrangement is described in 1%–4% of adult RCC.[74] The clinical behavior of TFE3-rearranged RCC is highly variable, ranging from slowly to rapidly progressive.[75] These tumors are well known for their reduced mutational load, TFE3 being among the few identified mutations.[76] The role of TFE3 is not totally understood, but its full oncogenic potential is realized by fusion with other genes that allow it to avoid being sequestered in cytoplasm and to be translocated into the nucleus.[77] From a retrospective analysis of 22 patients from different datasets, TFE3-rearranged RCC showed a higher objective response rate (ORR) with ICI than with TKI (25.0% with ICI vs 0% with TKI; $p=0.220$) and longer overall survival (62.4 months with ICI vs 10.3 months with TKI; $p=0.267$). Among TKI, cabozantinib is the only viable option since a retrospective analysis of 24 patients showed a 62.4% DCR, with a median PFS of 8.4 months and a median OS of 17 months.[78]

TFEB-altered RCC

TFEB rearrangement is typical of t(6;11) translocations[79,80] and is far less common than the TFE3-rearranged RCC, with approximately 80 cases reported.[75] The TFEB gene is often fused by translocation with the gene MALAT1. TFEB-rearranged RCC has indolent behavior.[81] Due to its rarity, clinical features and response to therapy of this neoplasm are difficult to describe. However, in the preclinical setting, it has been demonstrated that TFEB mediates immune evasion and resistance to mTOR inhibition via induction of PD-L1 expression.[82] Therefore, there could be room for the use of ICI plus mTORi combinations.

TFEB amplification is another rare occurrence, improperly associated with translocation. This alteration may or may not be due to a translocation. Only a few cases are reported in the literature, but they are far more aggressive than TFEB-rearranged RCC.[83,84] TFEB amplifications have shown an association with VEGFA (Vascular endothelial growth factor A) amplification or increased VEGFA expression.[85] Therefore, VEGFR targeting agents could be the more viable choice, as described in a small case series.[86]

Fumarate hydratase-deficient RCC

Fumarate hydratase-deficient RCC is the new denomination of Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) syndrome-associated RCC. This change was introduced to include also sporadic forms. Nonetheless, the diagnosis of FH-deficient RCC should alert the clinician to initiate the search for germline FH mutations, and thus the related genetic counseling.

In these tumors, fumarate is accumulated and its increased concentration results in inhibition of the prolyl-hydroxylase enzymes that target the Hypoxia Inducible Factor (HIF) for degradation. This results in activation of the hypoxia response, with induction of Vascular endothelial growth factor (VEGF) and VEGFR. In a recent genomic profiling study that focused on this rare type of RCC, Epithelial growth factor receptor (EGFR) signaling has been described to be increased and to promote glycolysis through the PI3K/AKT or MAP-kinase pathway.[87]

From a clinical viewpoint, this tumor has high metastatic potential. Retrospective data of patients with fumarate hydratase-deficient RCC treated with RCC's standard therapies show that ICI monotherapies offer better chances of disease control over TKI monotherapies.[87] At present, the major clinical trial for this neoplasm is a prospective phase II trial evaluating the combination of the EGFR blocker erlotinib and the anti-VEGF antibody Bevacizumab in 41 patients, most of which treatment-naïve. An ORR of 51%, a median PFS of 14.2 months, and a manageable safety profile were reported, with better outcomes for patients with HLRCC syndrome.[88] Other possible therapeutic options proposed for this neoplasm, based on in vitro evidence, are therapies targeting heme oxygenase 1, such as zinc protophorphyrin or an imidizaole-based inhibitor SLV-11199,[89] arginine deprivation,[90] and immunotherapies targeting the PD1-PDL1 axis.[91]

SDH-deficient RCC

The SDH-deficient RCC almost always involves SDH germline mutations, with

Succinate dehydrogenase B (SDHB) being the most common.[92,93] While low-grade SDH-deficient RCCs have a low risk for metastasis, high-grade tumors often are diagnosed in the metastatic stage.[92] Due to the rarity of this disease, clinical evidence is scarce. However, due to the overlap of the pathways enhanced by SDH deficiency and the Von Hippel-Lindau tumor suppressor (VHL) pathway, TKI could be an option.[94]

SMARCB1-deficient medullary RCC

This set of entities nearly replaced the old medullary RCC. It is often metastatic at presentation, with a very poor prognosis and a median overall survival of 13 months.[95] It is characterized by the loss of the chromatin modulator SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1, also known as INI1),[96] which leads to high expression of the Myelocitoma proto-oncogene (MYC) oncogene.[97] To date, platinum-based chemotherapy is the standard of care for first-line therapy in metastatic patients.[98] However, preclinical evidence[99] suggests a potential SMARCB1-deficient RCC sensibility for combinations of chemotherapy and a proteasome inhibitor. This has been confirmed in a small retrospective cohort, receiving the first-generation proteasome inhibitor Bortezomib, alternated with platinum-based chemotherapy.[100] Moreover, proteasome inhibitor Ixazomib is being tested in combination with gemcitabine and doxorubicin in patients with medullary RCC (NCT03587662).

Another therapeutic target could be EZH2, a catalytic subunit of the polycomb repressor complex 2 (PRC2),[101] which usually antagonizes the SWI/SNF complex. Currently, a phase II clinical trial is evaluating the Enhancer of zeste homolog (EZH) inhibitor tazemetostat in patients with SMARCB1-negative tumors (including RCC) (NCT02601950).

ALK-rearranged RCC

ALK is classically known as lung oncogene. ALK-rearranged RCC however exists and is a rare subtype, accounting for less than 1% of RCC.[102]

From a medical oncologist's viewpoint, ALK targeting should be the principal therapeutic strategy. However, even the rarity of this neoplasm makes it nearly impossible to obtain high-quality clinical data. In a case report, entrectinib—a multi-kinase inhibitor targeting ALK, ROS1, TrkA, TrkB, and TrkC—has shown a long-lasting objective response.[102] A recent systematic review highlights the effectiveness of different ALK inhibitors in pretreated ALK-rearranged RCC.[103]

ELOC (formerly TCEB1)-mutated RCC

Elongin-C (ELOC) is a subunit of the transcription factor B (SIII) complex and a part of the VHL complex. Its loss of function impairs the binding of HIF to the VHL complex, thus preventing HIF degradation.[104] ELOC-mutated RCC is a rare RCC subtype, with typical non-aggressive behavior, and its surgical removal is often curative.[105] However, the determination of ELOC status in the age of adjuvant therapies for RCC could be a criterion to avoid unnecessary treatments in radically resected patients.

Discussion

Non-clear cell RCC is a wide definition, comprising many entities, each one with specific histopathologic and genetic findings. In the past years, the low incidence and heterogeneity of nccRCC have determined the lack of trials addressing optimal strategies for each subtype. Most data were extracted from subgroup analyses of randomized trials including mainly ccRCC and a small proportion of nccRCC, single-arm phase II trials, nominal therapeutic use programs, and retrospective analyses. Approved treatments for ccRCC were transposed to non-clear cell histologies, although available meta-analyses[106,107] had confirmed that patients with nccRCC benefited less from VEGFR and mTOR inhibitors than those with ccRCC in terms of ORR, PFS, and OS. The efficacy of ICI monotherapy[24,25] and ICI plus ICI combination[9,108] for nccRCC proved to be modest. Lee and colleagues[11,12] conducted a phase II study to evaluate the combination of cabozantinib and nivolumab in nccRCC. The trial included two patient cohorts: cohort 1, consisting largely of pRCCs, but also translocated and unclassified RCC, reached its primary endpoint with promising efficacy and was subsequently expanded, while cohort 2, consisting of chRCCs was closed early due to a lack of objective responses and slow accrual. In cohort 1, ORR was 47.5%, mPFS of 12.5 months, and mOS was 28 months, a historical result for nccRCC. The results of the ancillary genomic study are remarkable. Patients in cohort 1 who had mutations such as CDKN2a, NF2, SETD2, FH, and BAP1,

which are frequent in nccRCC and have historically been attributed a negative prognostic role, achieved a relevant radiological response to combination treatment. Further studies are required to determine whether these mutations can reliably predict response to ICI/VEGFRi combinations. Similar efficacy data come from the KEYNOTE B61 trial,[13] which evaluated the combination of pembrolizumab and lenvatinib, reporting the highest mPFS among all the nccRCC trials (18 months, OS not reached). This trial showed an overall objective response rate of 49% among the entire nccRCC population, but chRCC was the subtype with the lowest ORR (28%). Based on the aforementioned single-arm phase II trials, the ICI-TKI combinations demonstrated a challenging ORR in the pRCC cohort and a promising ORR, mPFS, and mOS benefit in the overall nccRCC population.

Given the unique nature of each nccRCC subtype, genotyping of these tumors is crucial for developing targeted therapeutic strategies. Our review provides a current overview of molecular alterations of clinical interest that have been identified in nccRCC (Figure 1). Genomic characterization of pRCC has led to the identification of MET gene alterations and promoted the use of MET inhibitors. The randomized phase II SWOG 1500 trial,[5] also known as the PAPMET trial, confirmed that VEGF and MET signaling pathways are crucial and synergistic in the oncogenesis of pRCC. Cabozantinib, a multikinase inhibitor targeting MET, RET, AXL, VEGFR2, FLT3, and c-KIT, resulted in a higher objective response rate (23% vs 4%) and PFS benefit (9.0 months vs 5.6 months) compared to sunitinib, regardless of MET status.[5] Subsequently, in phase III SAVOIR trial,[22] a biomarker-driven strategy was explored to assess whether a more selective MET inhibitor (METi), savolitinib, could have higher activity in MET-driven pRCC. Savolitinib resulted in a higher objective response rate than sunitinib (27% vs 7%) but no statistically significant difference in PFS and OS.[22] The CALYPSO trial was the first to test the combination of an anti-PD-L1 ICI, durvalumab, with a selective MET inhibitor, savolitinib for the first-line treatment of nccRCC. METi plus ICI combinations are very attractive and will be explored further in the near future. Several trials are currently ongoing, among them: durvalumab plus savolitinib in MET-driven pRCC[59] and zanzalintinib, a multikinase inhibitor targeting VEGFR2, MET, AXL and other receptors, in combination with nivolumab in a large nccRCC cohort.[33] However, these trials have several limitations: most of them are single-arm phase II trials, thus lacking a comparison with a standard of care, or the comparator arm (sunitinib monotherapy) is not representative of current clinical practice. Although sunitinib has been the first-line standard of care for many years and its efficacy and manageability have been extensively demonstrated in real-world clinical practice,[109–111] today it is no longer the first choice option for frontline treatment of metastatic nccRCC. On the other hand, the data supporting the efficacy and manageability of cabozantinib in real-world settings are robust and steadily increasing.[15,112] Unfortunately, no prospective randomized trials with targeted therapies have been performed specifically in chRCC and mdRCC patients. For chRCC, the standard of care in the near future might be the ICI plus VEGFR-TKI combination, as suggested by recent trials,[11–13] although the activity rate is lower than pRCC. However, given the frequent mTOR mutations in this entity, mTOR inhibitors could be considered in combination with VEGFR-TKI in the first line,[23] and as monotherapy in subsequent lines of treatment. Regarding cdRCC, in the single-arm phase II BONSAI trial,[73] cabozantinib showed promising but not yet satisfactory activity (ORR: 33%, mPFS: 4 months, mOS: 7 months).

Where molecular characterization could impact even more is in the mdRCC class. Many mdRCC cases have been misdiagnosed in the past, given their morphological features that often resemble more common histologies. Only an experienced pathologist and an appropriate molecular characterization can correctly diagnose mdRCC. Distinguishing TFE3 rearranged RCC from TFEB rearranged RCC by Fluorescence in situ hybridization (FISH) testing or RNA sequencing is paramount since TFE3 rearranged RCCs are aggressive in most cases, whereas TFEB rearranged RCCs are generally indolent. Both TFE3 and TFEB-altered RCC showed a poor response to ccRCC treatments, with a slightly higher sensibility to cabozantinib, with a 17% ORR.[113] A potential efficacy signal comes from the KEYNOTE-B61: out of six translocation RCCs enrolled, four had objective responses. The role of combinations in translocation RCC should be taken into account. Nevertheless, the path to appropriate treatment for these entities is strictly dependent on the development of specific fusion-protein inhibitors since the rearrangement event is the main driver in these

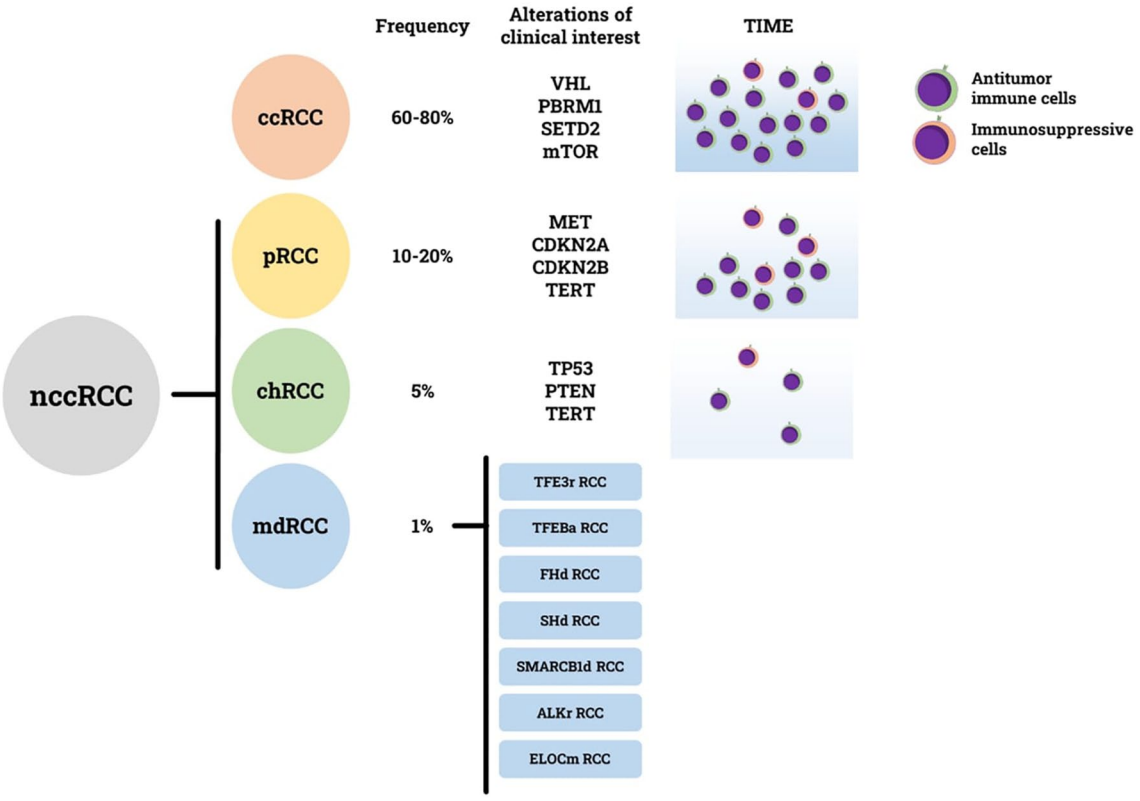

Figure 1. Principal molecular features in different subtypes of nccRCC. For every subtype relative frequency, alterations of clinical interest, and tumor immune microenvironment (TIME) composition are specified.

entities. Other examples of mdRCC whose diagnosis can be difficult are SDH-deficient RCC and FH-deficient RCC. Their identification is important because it promotes genetic counseling of patients and their relatives but can also be helpful in therapeutic choice. Patients with FH-deficient RCC could receive the combination of erlotinib and bevacizumab,[91] an option that does not preclude any of the other commonly available RCC therapies. The molecular definition could change the treatment of SMARCB1-deficient RCC. These entities, formerly known as medullary RCC, were treated with platinum-based chemotherapy, but their peculiar molecular asset shows a possible therapeutic window for proteasome inhibitors alternated with chemotherapy.[101] Some preclinical evidence hints at a possible therapeutic role of EHZ2 inhibitors.[114] Finally, another mdRCC that could be treated with a specific therapy is the ALK-rearranged RCC. The use of ALK-specific inhibitors was proven useful in this rare disease.[102]

Translating all these findings into clinical practice, however, is not easy. First of all, extensive molecular testing and WHO 2022 classification should be implemented in all centers. The analysis needed to fully characterize a molecular-defined RCC entity requires considerable skills and costs that could represent a major barrier, especially for smaller centers, or in developing countries. This problem can only be partially solved using cheaper techniques: for several nccRCC tumor types, diagnostic immunohistochemical stains can vicariate more expensive methods, such as in the case of INI1 loss in medullary tumors and FH loss staining in combination with gain of 2SC staining in FH-deficient tumors. Moreover, it should be considered that the nccRCC actionable mutations may not play a pivotal role. Gene expression analysis could integrate genomic profiling and highlight the effective role of each mutation. MET alterations (including MET amplifications, HGF amplifications, MET mutations, and chromosome 7 anomalies) have always been labeled as a driver in pRCC, but MET-specific inhibitors failed to overcome cabozantinib, which targets MET along with many other kinases. This means that, beyond preclinical evidence, solid clinical data derived from biomarker-driven trials—that evaluated all the

different alterations—and gene expression profiling data are necessary.

Gene expression profiling could also help to identify those patients who could benefit most from immunotherapy. In fact, RNA sequencing-based techniques allow the collection of data not only from cancer cells but also from tumor immune microenvironment (TIME), whose composition is strongly associated with response to ICI.[115] The study of TIME in nccRCC has only recently been addressed, but some key points are well established: unlike ccRCC, which usually has a large immune infiltrate, most pRCC show a less consistent infiltration, while most chRC shows no infiltrate at all (Figure 1). A particular case is medullary RCC, whose immune infiltrate is often conspicuous, but many of those cells are actually immunosuppressive cells.[116] Hence, a need for a personalized approach not only for target therapy but also for immunotherapy: whereas ccRCC benefits from classical ICI therapy, pRCC probably needs a treatment that increases immune infiltration, chRCC requires a strategy to build up the infiltrate, and medullary RCC need something to overcome immune suppression. All these tasks could be achieved by the introduction of new immunotherapies—such as ICI directed against non-classical targets (such as TIGIT, LAG3, ICOS), bispecific ICI, Toll-like receptor agonists, and adoptive immune cells—and their combinations with classical treatments.

Conclusion

Fortunately, in the near future, we will have more and more data on this unmet population. Considering the limited efficacy of current systemic therapies, enrollment into biomarker-driven clinical trials, and molecular characterization in clinical practice should be recommended for patients with nccRCCs. In addition, a better understanding of tumor immune microenvironment could lead to tailored immunotherapeutic strategies. The mutation- and TIME-driven strategy, rather than histology-driven, may be the best therapeutic approach to nccRCC (Figure 1).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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