Non-clear cell renal carcinomas: Review of new molecular insights and recent clinical data

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Abstract

Non-clear cell renal cell carcinomas (nccRCC) represent a highly heterogeneous group of kidney tumors, consisting of the following subtypes: papillary carcinomas, chromophobe renal cell carcinoma, so-called unclassified carcinomas or aggressive uncommon carcinomas such as Bellini carcinoma, renal cell carcinoma (RCC) with ALK rearrangement or fumarate hydratase-deficient RCC. Although non-clear cell cancers account for only 15 to 30% of renal tumors, they are often misclassified and accurate diagnosis continues to be an issue in clinical practice. Current therapeutic strategy of metastatic nccRCC is based primarily on guidelines established for clear cell tumors, the most common subtype, however this approach remains poorly defined. To date, published clinical trials for all histological nccRCC subtypes have been collectively characterized into one group, in contrast to clear-cell RCC, and given the small numbers of cases, the interpretation of study results continues to be challenging. This review summarizes the available literature for each nccRCC subtype and highlights the lack of supportive evidence from prospective clinical trials and retrospective studies. Future trials should evaluate treatment approaches which focus on a specific histological subtype and progress in treating nccRCC will be contingent on understanding the unique biology of their individual histologies.

Introduction

Renal cell carcinoma (RCC) affects almost 300,000 people worldwide each year and is responsible for more than 100,000 deaths annually. Understanding of RCC continues to rapidly evolve as new subtypes emerge, each characterized by distinct genomic and molecular alterations and variable responses to treatment, redefining the histological subtypes of kidney cancers [1]. In 2016, the revised World Health Organisation (WHO) renal tumor classification was published [2] to include these new rare renal tumor entities, however, the classification of some histological subtypes, such as the eosinophilic/oncocytic cell tumor group, is still under review [3]. Clear cell renal cell carcinoma (ccRCC) is the most common subtype, accounting for 70-75% of cases, and has been the focus of many large randomized and prospective phase III clinical trials (CheckMate 9ER, KEYNOTE-426, CheckMate 214) which have led to encouraging advances in treatment and clinical outcomes [4-8]. In contrast, non-clear cell renal cell carcinoma (nccRCC) is a highly heterogeneous group of kidney cancers, representing 15 to 30% of renal tumors, some of which are still undergoing classification according to limited evidence in the literature [2,3]. A total of 13 subtypes of non-clear cell tumors have been identified so far (**Table 1**). Some subtypes present a high metastatic potential such as carcinoma associated with the *MITF* translocation, type 2 papillary carcinoma, Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome-associated Renal Cancer (HLRCC), collecting (Bellini) duct carcinoma (CDC) or renal medullary carcinoma. Additionally, a number of these non-clear cell types are grouped collectively in the unclassified carcinoma subtype as they remain to be defined from a diagnostic and prognostic point of view [2]. It is important to note that tumors with a sarcomatoid component are found in both the ccRCC and nccRCC histological subtypes: it is a specific cell contingent with highly variable proportions within the tumor, and not a histological subtype. The presence of a sarcomatoid component is associated with aggressive metastatic behavior,

reduced survival and greater resistance to anti-angiogenic therapy [9,10]. Yet, recent data suggest a higher sensitivity to immune checkpoint inhibitors [8].

The non-clear cell subtype presents two major challenges, the first regarding diagnosis. These tumors are often misclassified since they are rare. In the CARARE cohort, review of a French national network for rare histological forms and patients under 40 years old, 31% of registered cases (n=539/1,719) were submitted as unclassified or difficult to diagnose. In all, only 2.7% of the cases (n=48) remained unclassified and reclassified cases accounted for 89% of the traditional RCC subtype and 11% of rare tumors.

The second challenge is therapeutic: although treating localized renal tumors is rarely difficult (with nephrectomy being the preferred radical therapy), treatment in the metastatic setting, based on recommendations established for clear cell tumors, is poorly defined and relatively little is known. Despite diverse biological characteristics, these subtypes are often classified in clinical trials as one global nccRCC entity and few studies have assessed the efficacy of systemic therapy for a specific nccRCC histological subtype. Due to limited clinical evidence, international guidelines recommend the use of the ccRCC therapies and investigation of targeted treatment options for these rare subtypes is currently ongoing [11,12] and few studies report recent data on clinical or biological characteristics, as well as systematic review of clinical research in patients with nccRCC cancer [13,14].

The objective of this article is to distinctly describe each nccRCC subtype, its molecular and histological basis, prognosis and, if available, evaluate recent data on current treatment therapies and ongoing clinical trials. This study does not review tumors with a sarcomatoid component.

Papillary renal carcinoma

Histological and molecular characteristics

Papillary renal cell carcinomas (pRCC) account for 15 to 20% of kidney cancers and are the most common subtype of nccRCC cases. pRCC is heterogeneous, with a variety of prognosis. Histological classification distinguishes pRCC into 2 biologically and clinically distinct types: type 1 and type 2. Diagnosing type 1 carcinomas is relatively well codified: from a clinical point of view they are rather indolent and are usually multifocal tumors. Histologically, they have a specific buff-yellow appearance, a papillary architecture and are composed of small cubic cells. Alterations of the *MET* pathway are very frequently observed. *MET* mutations are found in 13 to 15% of sporadic forms of these cancers, but the most frequent chromosomal aberration remains to be chromosomal gain, mainly on chromosomes 7 where the *MET* gene is located, and on chromosome 17. Overall, mutations of the *MET* gene or overexpression by gains of chromosome 7 are identified in 81% of subtypes 1. Rare splice variants have been reported in pRCC, as RNA transcript variants of *MET* lacking the canonical exons 1 and 2, but containing a novel exon 1 that splices to the canonical exon 3. Moreover, gene fusions involving *TFE3* or *TFEB* have also been observed in approximatively 15% of morphologic pRCC, and are certainly underdiagnosed in pRCC. Cases occur most often in children and young adults. While prognosis is usually favorable, the activation of the *MET* pathway is associated with high-grade tumors with a metastatic potential [15,16]. This pathway plays an important role in the pathophysiology in type 1 pRCC and could be a potential target for different therapeutic agents.

Type 2 pRCC is more heterogeneous and with a more complex diagnosis. Generally, type 2 pRCC have poorer prognosis than type 1 tumors, along with a higher grade and stage at diagnosis. It consists of tumors, which are very often unique, usually with an off-white appearance and often with

hemorrhagic and necrotic areas. Histologically, papillae are lined with large cylindrical cells with a multilayered nucleus. Genomically, these tumors are characterized by a frequent loss of the short arm of chromosome 9 (9p). Type 2 pRCC can be categorized into three distinct molecular subtypes. The first subtype shows a distinctive hypermethylation of *CDKN2A* promoter, found in 25% of type 2 and other subtypes [1,16]. These aberrations are associated with an overexpression of cell cycle genes and decreased overall survival. The second subtype shows mutations in chromatin remodeling-associated genes (*PBRM1, SETD2, BAP1*) with loss of arm 3p (*BAP1* and *PBRM1* being mutually exclusive). The last shows a hypermethylation of CpG islands (CpG island methylator phenotype (CIMP)) and is associated with the most pessimistic prognosis for type 2 pRCC and for all RCC subtypes [1]. It should be noted that 15% of type 2 pRCC may present a remodeling of *TFE3* or a loss of expression of fumarate hydratase (FH) which must therefore be systematically sought by the pathologist, since these alterations are associated with higher tumor aggressiveness [1,16]. The type 2 pRCC morphotype can be associated with the hereditary leiomyomatosis and demonstrate germline FH mutations with no alterations in the MET pathway. The prognosis of such tumors is very poor with early metastatic dissemination [17].

Clinical data

Papillary renal cell carcinomas are the most clinically evaluated subtype of nccRCC. Due to the low level of evidence from retrospective data in these rare and often misclassified tumors, only prospective trials that enrolled at least 12 patients with pRCC are reported here (**Table 2**). The first series of prospective trials evaluated anti-VEGF or mTOR tyrosine kinase inhibitors (TKI). Most of these trials investigated not only papillary tumors, but included patients with metastatic nccRCC, even if the results obtained specifically in papillary lesions were reported. In the phase II AXIPAP trial, which assessed the efficacy and safety of axitinib as a first-line treatment for patients with metastatic pRCC, the reported response rate was 28.6%. The median progression-free survival (PFS) was 5.6 months and overall survival was 18.9 months [18,19]. Conversely, the phase II SUPAP trial assessing sunitinib, reported a more disappointing response rate of 12% but similar survival rates [20]. Two randomized trials compared the efficacy of sunitinib versus everolimus in nccRCC [21,22]. Efficacy data for sunitinib are clearly superior in the ASPEN trial, but results for the ESPN trial are less convincing. Results with everolimus were disappointing in both phase II randomized trials as well as those obtained in the specific RAPTOR trial [21-23]. A non-planned subgroup analysis of a randomized phase III trial comparing temsirolimus to interferon in poor prognosis selected patients found more favorable results with temsirolimus [24]. A meta-analysis was performed in nccRCC to compare the effectiveness and toxicity of the different targeted therapies [25]. Although the papillary subtype was not specifically analysed, results suggest that sunitinib might be more effective, but with an enhanced toxicity profile. One important point, which may explain some of the differences in results among the studies identified, is verification of the histological diagnosis. Only four studies were centrally reviewed to confirm histology of the tumors: AXIPAP, SUPAP (on only 60% of the patients), RAPTOR and ESPN [19,20,22,23]. The rate of diagnosis review found in the studies varied from 5% in the AXIPAP trial to 20% in the RAPTOR trial [19,23]. As these studies did not conduct a central review, it is probable that 10 to 15% of the tumors were misclassified as papillary carcinomas.

Another interesting therapeutic target in papillary tumors is the MET pathway, as increasing evidence suggests that abnormalities occur frequently in this subtype. To better understand this pathway, several studies evaluate either EGFR and/or MET inhibitors, as they have been found to partly share the same cell receptor [26]. One recent study examined savolitinib specifically in papillary

tumors presenting an alteration of the MET pathway, regardless of the type (inactivating, fusion or amplification mutations) [27]. The global response rate was 7%, however interestingly, in subgroup analysis of patients with genomic abnormalities affecting the MET pathway, a higher response rate of 18% was found and PFS increased from 1.4 to 6.2 months. Based on this novel evidence, a phase III trial was subsequently conducted evaluating savolitinib and sunitinib in patients presenting locally advanced or metastatic papillary renal carcinoma with a *MET* alteration. However, this trial was prematurely discontinued for methodological reasons (ClinicalTrials.gov Identifier: NCT03091192). Recently, Pal et al published results from their phase II SWOG 1500 trial which compared the standard of care sunitinib to three other *MET* inhibitors (savolitinib, crizotinib and cabozantinib). Savolitinib and crizotinib arms were prematurely closed after a prespecified futility analysis. Final results from this study showed that cabozantinib was associated with improved PFS compared to sunitinib (9.0 vs 5.6 months, HR=0.60) and ORR (23% vs 4%) and providing evidence it should be considered as a new first line treatment for pRCC [28].

Four recent clinical trials were identified that explore new immunotherapy agents in nccRCC [29-32]. One agent, pembrolizumab monotherapy, has been shown to present interesting first-line antitumor activity for patients with metastatic nccRCC, particularly in those with papillary or unclassified histology, with a response rate of 25% in the papillary subtype [29]. Additional agents under investigation include Atezolizumab, which when combined with the anti-angiogenic agent bevacizumab, has been found to produce similar response rates as durvalumab combined with savolitinib [20,31]. And in the first prospective study of single agent Nivolumab in non-clear cell RCC, limited activity was seen in a pretreated papillary RCC population [32]. These results still remain to be confirmed.

In summary, even though papillary carcinomas are the most frequent histological subtype found among nccRCC, substantial challenges remain in the overall treatment landscape. Prospective trials evaluating specifically papillary carcinomas continue to be rare and often do not conduct central reviews to confirm the diagnosis, or undergo stratification by the subtype (1 *vs*. 2). New evidence suggests decreased efficacy of TKI targeting VEGF or mTOR inhibitors in papillary subtypes as compared to clear cell tumors.

As of March 2021, there are eleven ongoing trials investigating advanced papillary RCC publicly listed in the NCT clinical trial registry (https://www.clinicaltrials.gov/).

Chromophobe renal cell carcinoma

Histological and molecular characteristics

Chromophobe renal cell carcinoma (ChRCC) is the second most frequent subtype of nccRCC and accounts for about 5% of tumors. This subtype develops from the intercalated cells located in the cortical collecting ducts and involves multiple chromosomal losses affecting chromosomes 1, 2, 6, 10, 13, 17 or 21, and mutations of genes *P53, PTEN, TERT* [1,9,33,34]. In a study of gene expression profiling in RCC, the *KIT* oncogene was found to be upregulated specifically on the cell membranes of chromophobe RCC [35]. However, c-kit overexpression is not associated with *KIT* gene mutations in chRCC [36]. These carcinomas have a relatively good prognosis as only 5% are found to be metastatic [2]. And chromophobe tumors are among the so-called "cold" tumors, meaning mildly inflammatory or immunogenic [37,38]. ChRCC express the PD-L1 receptor weakly: in a study conducted on 101 patients with ChRCC, PD-L1 positivity in the tumor cells was detected in only 5% of the chromophobe RCC, in comparison to 10% in the papillary-type RCC, and 20 to 30% in the collecting ducts carcinomas or RCC of the *MITF* family (*TFE3/TFEB*) [37]. At this time, the chromophobe microenvironment appears to not be promising with regard to the development of immunotherapy agents targeting PD-(L)1.

Clinical data

From a clinical standpoint, very few prospective studies have specifically focused on patients with metastatic ChRCC. Often these tumors are grouped with other nccRCC tumors and in very scarce numbers, making the data difficult to interpret. And the only data available to date is from retrospective cohorts studies (**Table 3**). A retrospective study evaluating TKI efficacy in 45 ChRCC patients (65% were treated with sunitinib, 8% with sorafenib, 3% with pazopanib), exhibited a encouraging response rate of almost 30% [39]. These results were consistent with those found in another retrospective study, in which 10 patients treated with cabozantinib reported a treatment response rate of 30%. Regarding mTOR inhibitors, very little data was reported in this population and the number of cases included were even more limited (5 or 9 patients). Due to insufficient evidence, and limited knowledge regarding the natural history of disease, the safety and efficacy of mTOR inhibitor therapy in patients with ChRCC requires further research. Alternatively, combination therapies with mTOR inhibitors are currently ongoing, and bevacizumab plus everolimus combination has shown initial efficacy in patients with chromophobe tumors [40].

There exists even less evidence on available immunotherapy options, as very few provide response to treatment. For nivolumab, two retrospective studies and one prospective reported a null response rate for chromophobe tumors, confirming what has been previously observed at this level of immunological microenvironment [32,41,42]. And in a study, where only responses with pembrolizumab were reported, a low response rate of 9.5% was found, with two out of twenty-one patients experiencing responses to treatment [29]. Based on these results, immunotherapy approaches may have limited efficacy in ChRCC subtypes. Given their rare occurrence, future prospective trials will require a well-coordinated international network, to ensure of high quality and adequate sample sizes in the continued investigation of therapies for ChRCC.

MiTF family translocation renal cell carcinoma (*MiTF*-RCC)

Histological and molecular characteristics

MiTF-RCC (*microphthalmia-associated transcription factors*) were first characterized by their clinical presentation in primarily younger patients and the presence of overexpression of the TFE3 protein which belongs to the *MiTF* family of transcription factors.

Several subgroups have been identified by distinct genetic and morphological findings. Xp11 translocation renal cell carcinomas are characterized by specific cytogenetic abnormalities always involving the locus of the *TFE3* gene located on Xp11.2. Several translocations involving the Xp11.2 region have been described, among which two occur most frequently: translocation t(X;1)(p11.2;q21) and t(x;17)(p11.2;q25) which result respectively in fusion gene *PRCC-TFE3* (*papillary renal cell carcinoma*) and fusion gene *ASPL-TFE3* (*alveolar soft part sarcoma*). The fusion protein, including part of the *TFE3* gene, then acts as an aberrant intranuclear transcription factor, overexpressed compared to the native *TFE3* gene.

The histological presentation of Xp11 translocation RCC is heterogenous and its morphology often overlaps with characteristics of other RCC subtypes with papillary and clear cell architecture. Positive immunohistochemical staining with anti-*TFE3* antibody is a sensitive and specific marker, but identification of the *TFE3* rearrangement by FISH assays remains the current gold standard for diagnosis [43,44].

A second subgroup, the t(6;11) translocation carcinoma, is a rare variant showing a distinct translocation involving the locus for transcription factor *TFEB* located on chromosome 6p21 and leading to overexpression of the *TFEB* protein. The macroscopic and histological properties of this tumor are similar to Xp11 translocation carcinoma. Immunohistochemical staining of *TFEB* is a sensitive and specific marker and a *TFEB* break-apart FISH analysis allows molecular confirmation [45].

Clinical data

Xp11 translocation RCC comprises the largest subgroup of RCC in pediatric patients with a mean age of 17 years at diagnosis [46] and is present in about 1 to 4% of adult RCC cases with a mean age around 40 [44]. This number of cases is likely underestimated due to the morphological similarities seen in clear cell and papillary renal carcinomas. Argani et al reported translocation carcinoma in children who have received chemotherapy for malignancies, autoimmune disorders, or bone marrow transplant conditioning previously [47].

The outcome of Xp11 translocation RCC cases is highly variable with indolent and aggressive clinical courses found in each age group. It has been observed that carcinomas harboring the *ASPL-TFE3* fusion gene are diagnosed more often at an advanced stage with regional lymph node involvement, whereas cases of carcinoma harboring the *PRCC-TFE3* fusion gene subtype are reported with late recurrences appearing several decades after initial diagnosis [48].

Fewer than 100 cases of t(6;11) translocation carcinoma have been reported in the literature, primarily involving younger patients with a mean age of 34 years. Furthermore, the course of the disease seems to be more indolent than Xp11 translocation RCC or ccRCC with fewer than 10% of patients developing metastases [49].

To date, no prospective studies on systemic treatment of MiTF-RCC have been conducted. Several cases have been reported in retrospective studies and the results are dismal regarding VEGFR-targeting treatments, with a treatment response rate of 30% and median PFS of 7.1 to 8.2 months [50,51]. In a retrospective study, Thouvenin et al reported patients with MiTF-RCC treated with cabozantinib experienced a median PFS of 8.4 months over a median follow-up of 14 months,

suggesting cabozantinib could be a potential treatment option for *MiTF* RCC [52]. However further prospective trials are warranted to validate the best treatment strategy for this rare subtype.

The efficacy of immune checkpoint inhibitors in MiTF-RCC has been evaluated in one retrospective study. In this study, twenty-four patients were included and a response rate of 16.3% with a median PFS of 2.5 months was reported [53].

Unclassified carcinomas

Histological and molecular characteristics

Unclassified or undifferentiated RCC (uRCC) represent 2 to 6% of renal epithelial tumors in adults [54]. In the past few years, recognition of the diagnostic challenges for RCC presented by oncocytic/eosinophilic morphologies, has led to an expansion in the number of cases included in this category. According to the WHO 2016 classification, this diagnostic category includes renal tumors which do not fit any of the identified histological subtypes and includes relatively undifferentiated tumors. This designation also includes unclassified oncocytic cell tumors, or tumors with a pure sarcomatoid histology, whose clinical behavior can vary greatly. Diagnosis of these tumors remains one by exclusion, requiring systematic cytogenetic (FISH) or molecular (CGHa) analysis to rule out specific abnormalities of the other subtypes [2]. Genetic assessment indicates that 26% of uRCC show characteristic NF2 gene loss or mutations of genes *NF2* (18%), *SETD2* (18%), *BAP1* (13%), *KMT2C* (10%), and *MTOR* (8%) [55].

Clinical data

These tumors are particularly aggressive and are often metastatic at the time of diagnosis, even though low-grade tumors can readily be identified [54]. At present, uRCC specific clinical studies have not been conducted, but data identified within the few available prospective and retrospective trials, evaluating TKI-directed treatment in nccRCC, seem to show interesting results [21,22,56] (**Table 4**). Current immunotherapy approaches also seems promising, with response rates higher than 30% having been reported [29,41]. In summary, although the uRCC subtype can be found in many studies carried out with non-clear cell tumors (ranging from 6 to 15% cases), due to the lack of systematic central reviewing and wide histological spectrum, interpreting results remains delicate and no standard therapy has been established [21,22,56].

Aggressive uncommon carcinomas

Histological and molecular characteristics

Several very rare entities have been identified in recent years. Medullary carcinomas are extremely rare tumors (< 1%) and are usually misdiagnosed. Most of the time, they are discovered at an advanced stage or are metastatic from the start, in very symptomatic patients with poor clinical outcomes. On the macroscopic histological level, these are very white tumors, indurated and always medullary, more or less cortical. Special features to note include fibrous stroma with a tubular architecture. These tumors are further classified in two groups: collecting duct carcinoma (CDC), also called Bellini carcinoma, and "true" medullary carcinomas, identified mostly in patients presenting sickle cell anemia. In the latter, the tumors present the same histological and macroscopic appearance as the CDC, but have as specific characteristic an alteration in the number of copies with *SMARCB1* gene loss, resulting in a loss of expression of INI1 (not observed in Bellini carcinoma) [57].

CDC has a specific metabolic and immune profile: it is characterized by a specific molecular abnormality, namely inactivation of the genes involved in oxidoreductase activity, pyruvate metabolism and the tricarboxylic acid cycle. It also displays important intratumoral lymphocyte infiltration [58].

Other rare entities with an aggressive/metastatic potential

RCC subtypes with *ALK* rearrangement are usually located in the medulla, and cases primarily occur in young patients. These emerging types of tumors are composed of large eosinophilic cells with abundant cytoplasm, in which the nucleus displays a prominent nucleolus. Recently, screening and diagnosis have become increasingly important for this rare, but aggressive entity, as the potential efficacy of targeted therapies such as ALK inhibitors is currently being explored [3].

Fumarate hydratase-deficient RCC is another a very rare RCC and occurs in patients around 40 years old and presenting a solid complex architecture, papillary, cribriform and/or tubulocystic in form. Cells are eosinophilic frequently with voluminous nucleoli and immunostaining shows a loss of FH expression in the tumor cells. This RCC is to be associated with a hereditary autosomal dominant transmission: Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome-associated Renal Cancer (HLRCC), which in addition to renal cell cancers, is characterized by the development of cutaneous and uterine leiomyomas and leiomyomatas in patients presenting a germline mutation of the FH gene. Eighty-two percent of patients with HLRCC syndrome with FH mutation, affected by a carcinoma, are metastatic when diagnosed or will soon become so, with a median survival of 18 months [59].

Clinical data

These tumors represent a very heterogeneous group. Historically, they have often been treated with different chemotherapy regimens since partial response was observed, but not for long: prognosis is very poor with a median survival not exceeding 1 year [1,60]. Regarding targeted treatments, TKI-directed therapies are the preferred treatment, however only a few, very small trials have been carried out for this subtype [11,12]. The best treatment response rate reported to date is with cabozantinib: a retrospective analysis showed one response among four treated patients [56]. In a second study, no responses were observed in the treatment of patients in the ESPN prospective trial [22]. Regarding the investigation of immune-oncologic agents, PD-L1 positivity in tumor cells was detected in 20% of collecting duct carcinomas and could be of interest as a potential treatment target [37]. And as of recent, there is one prospective study involving 4 patients on nivolumab which reported a response in 1 patient [32]. Finally, the sign of mutation of the *NF2* signaling pathway seems to be associated with a sensitivity to mTOR inhibitors, but no study has been conducted on this topic thus far and no active trials focus on this specific subtype [61].

To summarise, patients with CDC are eligible for enrollment in non-clear cell tumors trials, but on average only one patient is included in each trial, thus making it impossible to draw any meaningful conclusions from these small sample sizes. Without specific trials that focus on each targeted therapy, obtaining clinically relevant data will continue to be difficult for this subtype. Moreover, unlike most other types of non-clear cell histologies, collecting duct RCCs may respond to cytotoxic chemotherapy using platinum-based chemotherapy as reported in several case reports and trials [62-66]. A specific study, the BEVABEL trial, combining chemotherapy and anti-angiogenics (bevacizumab) was conducted, however this study produced negative results, validating platinum-based chemotherapy as the standard of care [67].

To address other rare entities with aggressive potential, greater understanding of their underlying biological processes is necessary for the development of future therapeutic agents. Several potential therapeutic agents are currently under investigation (**Table 5**). Initial evidence suggests that RCC with ALK translocation might benefit from *ALK* inhibitors therapy. It is hopeful that ALK inhibitors could effectively improve the prognosis of advanced translocation-associated RCC involving *ALK* as recent case reports have showed a response to entrectinib or alectinib in patients with metastatic pRCC [68,69]. RCC with fumarate hydratase (FH) deficiency is characterized by a paradigmatic of oncometabolite-driven malignant transformation, with activation of hypoxia signaling (e.g., HIF) through α-ketoglutarate-dependent dioxygenases. This mechanism has been well characterized for isocitrate dehydrogenase in other tumor types, leading to the development of enzymatic inhibitors with antineoplastic properties (such as enasidenib and ivosidenib). Currently FH activating compounds are in clinical development in RCC [70,71].

Conclusion

NccRCC represents a biologically heterogeneous group of kidney tumors, with variable phenotype and genotypes. Despite advanced methods to identify and detect genetic abnormalities and increased knowledge of molecular pathways, accurate diagnosis nccRCC remains problematic, and appropriate clinical classification continues to be difficult. In practice, diagnosing these subtypes requires the expert opinion of a pathologist and networking, in particular for some subtypes such as ccRCC with a papillary architecture occurring before the age of 47, kidney tumors with oncocytic/eosinophilic cells or collecting duct/medullary RCC. Even though there is no standard treatment for nccRCC, sunitinib is the drug with the most safety and efficacy evidence in both retrospective studies and clinical trials, and represents the first-intent drug in international recommendations [11,12]. Treatment with temsirolimus, everolimus, pazopanib, axitinib and nivolumab are also considered as options [72]. Immunotherapy results are still too premature to inform and provide recommendations for updating current clinical practices. Additional targeted therapies have been or are being currently studied (**Table 5**). Elucidating the biological drivers and targetable vulnerabilities of these malignancies could represent an opportunity of personalized treatments.

Until recently, trials grouping all "non-clear cell" subtypes were conducted because they enabled more rapid inclusions. These trials, however, involve tumors presenting different oncogenesis, aggressivity, and profiles of gene and metabolic expression, making the results difficult to extrapolate. Currently, specific trials are only conducted for the papillary subtype. In conclusion, developing specific multicenter and potentially international trials for each subtype must be a priority, in order to define better therapeutic strategies; all guidelines recommend this [11,12].

Author contributions

P. Barthelemy, N. Rioux-Leclercq, S. Negrier contributed to the development of the outline, drafted, revised, and edited the manuscript. The rest of the author group reviewed the manuscript.

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TABLES

Table 1

Non-clear cell renal cell cancer (nccRCC) classification [2]

Non-clear cell renal carcinomas: 15 to 30%
Renal multilocular cystic neoplasia with low malignant potential
Carcinoma associated with *MiTF* translocations
Chromophobe cell carcinoma
Papillary renal carcinoma
Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome-associated Renal Cancer
Collecting (Bellini) duct carcinoma
Renal medullary carcinoma
Carcinoma associated with succinate dehydrogenase (SDHB) deficiency
Mucinous tubular and spindle cell carcinoma
Tubulocystic carcinoma
Acquired cystic disease-associated carcinoma
Papillary clear-cell renal cell carcinoma
Unclassified carcinoma

Table 2

Papillary CCR: efficacy data from prospective trials

	Targeted therapy (trial name)	N pap/total	Response Rate	Median PFS (months)	Median OS (months)	Ref.
TKI anti VEGF or mTor						
VEGFR TKI	Axitinib (AXIPAP)	44 12 30	26.2%	5.6 type 1: 4.8 type 2: 5.5	18.9 type 1: NR type 2: 17.4	[19]
VEGFR TKI	Sunitinib (SUPAP)	15 46	12%	type 1: 6.6 type 2: 5.5	type 1: 17.8 type 2: 12.4	[20]
VEGFR TKI	Sunitinib	22/31	23.5%	6.4	NR 40 % at 1y	[73]
VEGFR TKI	Sunitinib	27/57	0%	1.6	12.6	[74]
VEGFR TKI *vs.* mTOR Inhibition	Sunitinib *vs.* Everolimus (ASPEN)	70/108	24% *vs.* 5%	8.1 *vs.* 5.5	31.5 *vs.* 13.2	[21]
VEGFR TKI *vs.* mTOR Inhibition	Sunitinib *vs.* Everolimus (ESPN)	27/68	7% *vs.* 0%	5.7 *vs.* 4.1	16.6 *vs.* 14.9	[22]
mTOR Inhibition	Everolimus (RAPTOR)	44 (PP)	1% (pop ITT, n=88)	type 1 (n=8): 5 type 2 (n=30): 4	type 1 (n=8): 17.8 type 2(n=30): 20.5	[23]
mTOR Inhibition	Temsirolimus vs. Interferon †	30/25	NA	5.9 vs. 2.1	7.8 vs.5.7	[24]
MET or EGFR inhibitors						
EGFR TKI	Erlotinib	45	11%	NA	27	[26]
cMET Inhibition	Savolitinib In MET driven tumors	109 44	7% 18%	1.4 6.2	NA NA	[27]
cMET Inhibition	Cabozantinib	44	23%	9.0	NA	[28]
cMET Inhibition and VEGFR Inhibition	Foretinib In Met germline mutation	74 10	13.5% 50%	9.3 NA	70% at 1y NA	[75]
cMET & EGFR Inhibition *vs.* cMET Inhibition	Tivantinib *vs.* Tivantinib & Erlotinib	50	0% *vs.* 0%	2 *vs.* 3.9	10 *vs.* 11.3	[76]
cMET Inhibition	Crizotinib* (CREATE)	23	17%	41.6% at 2 y	53.2% at 2 y	[77]
Immune Checkpoint Inhibitor						
Anti-PD1 Antibody	Pembrolizumab	118/165	28%	4.1	74% at 1y	[29]
Anti-PD1 Antibody	Nivolumab	29/50 Type 1 : 20 Type 2: 9	 5% 11%	NA	NA	[32]
Anti-PDL1 Anti VEGF antibodies	Atezolizumab +Bevacizumab	36/52	25%	NA	NA	[30]
cMET Inhibition and PDL-1 antibody	Savolitinib +Durvalumab (CALYPSO)	41	27%	4.9	12.3	[31]

Trials on a grey background have included only papillary tumors.

NA: not applicable; NR: not reached; pap: papillary; PFS: progression-free survival; OS: overall

survival.

* In mPRCC type 1 only † In patients with poor prognosis

Table 3

Chromophobe CCR: efficacy data from prospective and retrospective trials

Targeted therapy (trial name)	Type	N ChRCC/total	Response rate	Median PFS (months)	Median OS (months)	Ref.
TKI anti VEGF						
Sunitinib (ASPEN)	Prospective	10/108	10%	5.5	NA	[21]
Sunitinib (ESPN	Prospective	6/68	NA	8.9	31.6	[22]
Cabozantinib	Retrospective	10/112	30%	NA	60% at 1 y	[56]
TKI	Retrospective	47/61	28.9%	8.7	22.9	[39]
anti VEGF + mTor inhibitors						
Lenvatinib Everolimus	Prospective	9/31	44,4%	NA	NA	[78]
Bevacizumab/Everolimus	Prospective	5/34	40%	NA	NA	[40]
mTor inhibitors						
Everolimus (ASPEN)	Prospective	6/108	33%	11.4	NA	[21]
Everolimus (ESPN)	Prospective	6/68	NA	NA	25.1	[22]
Everolimus	Prospective	8	25%	13.1	21.6	[79]
mTOR	Retrospective	11/61	0%	1.9	3.2	[39]
Immune Checkpoint Inhibitor						
Nivolumab	Retrospective	5/41	0%	NA	NA	[41]
Nivolumab	Prospective	9/50	0%	NA	NA	[32]
Ipilimumab/Nivolumab	Retrospective	5/18	0%	NA	NA	[42]
Pembrolizumab	Prospective	21/165	9.5%	NA	NA	[29]

NA: not applicable; PFS: progression-free survival; OS: overall survival.

Table 4

Unclassified CCR: efficacy data from prospective and retrospective trials

Targeted therapy (trial name)	Type	N Uncl/total	Response Rate	Median PFS (months)	Median OS (months)	Ref.
TKI anti VEGF						
Sunitinib (ASPEN)	r	8/108	0%	11.5	NA	[21]
Sunitinib (ESPN)	Prospective	4/68	NA	9.4	15.4	[22]
Cabozantinib	Retrospective	15/112	13%	NA	36% at 1 y	[56]
mTor inhibitors						
Everolimus (ASPEN)	Prospective	14/108	7%	5.5	NA	[21]
Everolimus (ESPN)	Prospective	6/68	r	rr	NA	[22]
Immune Checkpoint Inhibitor						
Nivolumab	Retrospective	14/41	36%	NA	NA	[41]
Nivolumab	Prospective	4/50	25%	NA	NA	[32]
Ipilimumab/Nivolumab	Retrospective	3/18	1/18	NA	NA	[42]
Pembrolizumab	Prospective	26/165	34.6%	NA	NA	[29]

NA: not applicable; Uncl: unclassified; PFS: progression-free survival; OS: overall survival.

Table 5

Ongoing trials in nccRCC.

NCI Trial ID	Histology	Treatment	Comments	ref.
NCT01130519	Papillary or HLRCC	Bevacizumab + erlotinib	Ongoing	[80]
NCT02019693	Papillary	Capmatinib	Ongoing	[81]
NCT02363751	Collecting Duct Carcinoma	Gemcitabine + platinum + bevacizumab	Ongoing	[82]
NCT02495103	Clear cell and non-clear cell	Vandetanib + metformin	Ongoing	[83]
NCT02626130	Clear cell and non-clear cell	Tremelimumab with/without cryoablation	Ongoing	[84]
NCT02724878	Non-clear cell	Atezolizumab + bevacizumab	Ongoing	[85]
NCT02761057	Papillary	Cabozantinib vs. crizotinib vs. volitinib vs. sunitinib	Ongoing	[86]
NCT02819596	Clear cell and Papillary	Durvalumab ± savolitinib ± tremelilumab	Ongoing	[87]
NCT02915783	Non-clear cell	Lenvatinib + everolimus	Ongoing	[88]
NCT03075423	Non-clear cell	Ipilimumab + nivolumab vs. sunitinib	Ongoing	[89]
NCT03274258	Renal medullary carcinoma, RCCU-MP, and kidney malignant rhabdoid tumors	Nivolumab + ipilimumab or nivolumab + NKTR214	Ongoing	[90]
NCT03319628	Papillary RCC and other solid tumors	XMT-1536	Ongoing	[91]
NCT03635892	Non-clear cell	Nivolumab + Cabozantinib	Ongoing	[92]
NCT03685448	ANZUP Non clear Cell	Cabozantinib post immuno	Ongoing	[93]
NCT02619253	Clear cell and non-clear cell	Pembrolizumab + vorinostat	Ongoing	[94]
NCT02721732	Rare Tumors	Pembrolizumab	Ongoing	[95]
NCT02915783	Non-clear cell	Lenvatinib + everolimus	Ongoing	[96]
NCT03091192	Papillary	Savolitinib vs. sunitinib	Ongoing	[97]
NCT03117309	Clear cell and non-clear cell	Nivolumab and nivolumab + ipilimumab	Ongoing	[98]
NCT03541902	Non-clear cell	Cabozantinib vs. sunitinib	Ongoing	[99]
NCT03587662	Renal medullary carcinoma, RCC unclassified with medullary phenotype, and kidney malignant rhabdoid tumors	Ixazomib, gemcitabine, and doxorubicin	Ongoing	[100]
NCT03177239	Non-clear cell	IPI/Nivolumab post-nivolumab	Ongoing	[101]

Highlights

- Non-clear cell renal cell carcinomas (nccRCC) are highly heterogeneous tumors.
- These tumors are often misclassified.
- The therapeutic strategy of metastatic nccRCC remains poorly defined
- Few prospective clinical trials are available, most of them mix all nccRCC subtypes
- Developing specific trials for each histological subtype should be a priority.