Non–Clear Cell Renal Cell Carcinomas: Biological Insights and Therapeutic Challenges and Opportunities

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Abstract: The non–clear cell renal cell carcinomas (nccRCCs) are a diverse group of rare-variant renal carcinomas. Each subtype harbors a distinct cell of origin and exhibits a distinct clinical behavior and response to therapy. The advent of next-generation sequencing has drastically advanced our understanding of key genetic and epigenetic drivers in these tumors, although mechanistic studies are needed to elucidate pathogenesis. The only 2 randomized clinical trials in nccRCC included patients with diverse histologic subtypes. Both of these trials compared everolimus with sunitinib and provided evidence suggesting that frontline sunitinib is superior to everolimus in terms of progression-free survival. Renal medullary and collecting duct carcinomas do not respond to targeted agents, supporting the use of platinum-based chemotherapy as frontline therapy. Clinical evidence is currently emerging on the efficacy of c-MET inhibitors in patients with papillary type 1 RCC harboring germline c-*MET* mutations. Data on the activity of immune checkpoint inhibitors in this setting are lacking; however, several trials are ongoing in this space. The management of patients with nccRCC likely will improve in the future with histology-driven trials, which may pave the way for personalized therapies based on the molecular characterization of these orphan kidney cancer subtypes. Efforts must also be made to establish in vitro and animal models for testing hypotheses generated through extensive genomic analysis. Ultimately, collaborative national and international studies are urgently needed to improve therapeutic strategies in patients with metastatic disease.

Introduction

In the European Union, there were approximately 59,000 new cases of kidney cancer and 26,000 disease-specific deaths in 2012.[1] The incidence is similar in the United States, with approximately 63,000 new cases reported in 2016.[2] Among patients with malignant tumors of the kidney, non–clear cell renal cell carcinomas (nccRCCs) account for approximately 25% of cases. Approximately 30,000 patients per year are candidates for systemic therapy in the

European Union alone, of whom an estimated 7000 have tumors with non–clear cell histology.[2] nccRCCs arising from different cells of the nephron exhibit diverse histologies associated with distinct clinical behaviors. In the 2016 World Health Organization (WHO) classification of kidney tumors, 13 subtypes of nccRCC are identified: multilocular cystic renal neoplasm of low malignant potential, papillary RCC, hereditary leiomyomatosis and RCC syndrome–associated RCC, chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, MiT family translocation RCC, succinate dehydrogenase–deficient renal carcinoma, mucinous tubular and spindle cell carcinoma, tubulocystic RCC, acquired cystic disease–associated RCC, clear cell papillary RCC, and unclassified RCC.[3]

Unfortunately, despite their unique biological behaviors, all these subtypes are lumped together as nccRCC when they are compared with clear cell renal cell carcinoma (ccRCC) in clinical trials. Indeed, only a handful of clinical trials reported to date have investigated the efficacy of chemotherapy or targeted agents in a specific histologic subtype of nccRCC. This type of research is currently evolving with the implementation of next-generation sequencing, which has allowed exploration of the genetic landscape of some of the subtypes—although much is not understood about their intra- and inter-heterogeneity. The first part of this review focuses on the cells of origin of these kidney tumors and discusses new insights based on next-generation sequencing and the identification of key alterations. The second part discusses available clinical trial data and provides a perspective on novel trials and the management of nccRCC.

Ontogenesis of Non–Clear Cell Renal Cell Carcinoma

At least 10 distinct cell types make up the proximal and distal parts of the nephron; thus, the various subtypes in the diverse group of RCCs exhibit different histologic features and biology.[4] Recently, using DNA methylation profiling, we (Drs Malouf and Tannir) reported that oncocytoma and chromophobe tumors cluster together, suggestive of a cell of origin within distal cells of the nephron.[5] Our data are consistent with the chromophobe data from The Cancer Genome Atlas (TCGA), which also investigated the ontogenesis of these tumors.[6] In addition, using DNA methylation signatures, we found that translocation RCCs and mucinous and spindle cell carcinomas cluster together with clear cell and papillary RCCs, consistent with a cell of origin within the proximal tubule.[5] Using transcriptome analysis, we recently demonstrated that collecting duct carcinomas may arise from the distal convoluted tubule of the kidney.[7] In renal medullary

carcinoma, immunohistochemical staining indicates that this rare and aggressive tumor may arise from the distal part of the nephron, likely within the collecting duct. Interestingly, all types of RCC may be associated with sarcomatoid dedifferentiation, suggesting that sarcomatoid features are a marker of high-grade and aggressive RCC rather than a distinct histopathologic subtype.[8] Given all these data, future efforts to understand RCC ontogenesis should focus on the microdissection of kidney cells and an integrative analysis of their transcriptome and epigenetic features.

Molecular Biology of Non–Clear Cell Renal Cell Carcinoma

As previously discussed, each subtype of nccRCC is characterized by a unique signature and often harbors genetic aberrations distinct from those of clear cell RCC, which typically harbors *VHL* aberrations.[9] This review focuses on the most frequent nccRCC subtypes, which were recently characterized through TCGA.

Papillary Renal Cell Carcinoma

Papillary RCCs are a heterogeneous group of tumors that pathologists usually divide into papillary type 1 and papillary type 2 subtypes.[10] The biology and natural history of these groups are completely different. Papillary type 1 tumors usually have an indolent course, whereas papillary type 2 tumors are more aggressive. Historically, germline mutation of the c-*MET* gene leading to its constitutive activation has been described in families with hereditary papillary RCC.[11] Even when they are sporadic, 10% to 21% of papillary type 1 tumors harbor somatic c-*MET* mutations.[11-13] Likewise, papillary type 2 disease is usually described in patients with hereditary leiomyomatosis and RCC, which confers a predisposition to an aggressive form of type 2 papillary RCC caused by germline mutation of the gene encoding fumarate hydratase (*FH*), an enzyme in the tricarboxylic acid cycle.[14] With the advent of next-generation sequencing, TCGA undertook major efforts that characterized 161 cases of papillary RCC: 75 papillary type 1, 60 papillary type 2, and 26 unclassified papillary tumors.[15] The study identified previously described somatic mutations of c-*MET* in papillary type 1 tumors in 17% of cases. In addition, the study revealed several novel findings, particularly in the classification of papillary type 2 tumors, which were divided into 3 distinct subgroups on the basis of molecular differences associated with patient outcome.[15] In particular, type 2 tumors were characterized by *CDKN2A* silencing, mutations in chromatin-modifying genes (*SETD2*, *BAP1*, or *PBRM1* mutations are associated with a high rate of *TFE3* or *TFEB* fusion), or a CpG island methylator phenotype

(CIMP; characterized by poor survival and mutation of the *FH* gene).[15] Interestingly, beyond *MET* and *FH* mutations, somatic mutations were also identified in the Hippo and NRF2 pathways as well as in chromatin modifiers, including members of switch/sucrose nonfermentable (SWI/SNF) complex.[15] The relevance of these mutations is still unclear.

Chromophobe Renal Cell Carcinoma

Chromophobe RCCs account for fewer than 5% of kidney tumors and usually exhibit indolent behavior. Only 1.3% of patients have distant metastases at diagnosis.[16] Chromophobe RCC is associated with germline mutation of the folliculin gene (*FLCN*) in Birt-Hogg-Dubé syndrome[17] and with germline mutation of *PTEN* in Cowden syndrome.[18] Until recently, the genomic basis of chromophobe RCC occurring sporadically was unknown. TCGA consortium recently reported on an integrative analysis of 66 cases of chromophobe RCC; it identified a profound change affecting mitochondrial function as a hallmark of the disease biology, which was characterized as relying on oxidative phosphorylation.[6] The most frequent somatic mutations in chromophobe RCC were related to *TP53* and *PTEN* genes and affected 32% and 9% of the tumors, respectively. Mutations in the mammalian target of rapamycin (*mTOR*) gene occurred in 23% of chromophobe RCCs; however, the significance of these mutations regarding response to therapy is unknown. Finally, both mutations in the telomerase reverse transcriptase promoter (*TERT*) gene and genomic rearrangements within the TERT promoter region were observed.[5] However, the driving events in aggressive vs indolent cases remain undetermined and deserve further study.

MITF Translocation Renal Cell Carcinoma

Translocation RCC is a rare subtype of RCC that was introduced in 2004 as a genetically distinct entity in the WHO classification of kidney tumors. It accounts for one-third of pediatric RCC cases and almost 15% of RCC cases in patients younger than 45 years.[19] The most frequent translocations involve the *TFE3* (Xp11.2) and *TFEB* (6p21.1) genes, discovered almost 2 decades ago.[20] Recent analysis of TCGA cohorts with clear cell and papillary type 2 RCC identified misclassified translocation RCC in 1.5% and 12% of cases, respectively.[21,22] In addition, comprehensive analysis of several nccRCC subtypes identified *MITF* (3p13) translocation in a subgroup of papillary RCCs, expanding the spectrum of the disease.[23] Of note, *TFE3*, *TFEB,* and *MITF* can fuse with different partners, although the role of those partners in carcinogenesis remains unknown. Recently, virtual karyotyping revealed a range of phenotypes in translocation RCC, including some cases harboring clear cell RCC or papillary RCC patterns and

pediatric cases harboring a normal karyotype.[24] Of note, aggressive translocation RCC in adults was characterized by gain of 17q, and this was induced through multiple mechanisms.[24] Translocation RCC displays a unique gene expression signature in comparison with other RCC subtypes. In addition to the driving translocation, a high rate of mutations in chromatin-modifying genes was identified in translocation RCC, but these did not overlap with the mutations commonly seen in ccRCC, such as those of *VHL*, *PBRM1,* and *BAP1*.[21]

Collecting Duct Carcinoma

Collecting duct carcinoma, also known as Bellini duct carcinoma, is a rare subtype of kidney tumor that is thought to arise from the distal part of the nephron within the collecting duct. The diagnosis of collecting duct carcinoma is challenging because the differential diagnosis includes renal medullary carcinoma and upper-tract urothelial carcinoma. Recent transcriptomic analysis of collecting duct carcinoma identified a unique gene expression signature of this subtype among other kidney carcinomas, and this was consistent with a putative cell of origin within the distal convoluted tubule.[7] Furthermore, transcriptomic signature identified metabolic shift with impairment of oxidoreductase activity and the tricarboxylic acid cycle, as well as an immunogenic response consistent with tumor-infiltrating lymphocytes.[7] In addition, *SLC7A11*, a cisplatin resistance–associated gene, was identified as being overexpressed in 80% of collecting duct carcinoma tumors.[25] At the genetic level, 2 studies investigated genomic aberrations in collecting duct carcinoma. The first study reported on targeted sequencing of 17 cases and identified frequent somatic mutations in the *NF2* (29%), *SETD2* (24%), and *SMARCB1* (18%) genes; of note, *CDKN2A* also was deleted in 12% of cases.[26] The second study reported on a smaller number of cases and identified frequent deletions of *CDKN2A* (62.5%), with only a recurrent mutation in the *MLL* gene in 2 of 4 cases assessed by exome sequencing.[25] Larger studies are needed to clarify the role of driver mutations in this aggressive disease.

Renal Medullary Carcinoma

Renal medullary carcinoma has long been described as the seventh nephropathy in sickle cell disease, although this dogma recently has been challenged.[27] For reasons that remain unknown, renal medullary carcinoma predominantly affects patients with sickle cell trait, particularly young patients of African descent. At the molecular level, renal medullary carcinoma is characterized by INI1 protein inactivation, and this is currently required to confirm the diagnosis. *INI1* is a chromatin-modifying gene that belongs to the SWI/SNF complex, which has recently been

described as highly mutated in ccRCC.[28] For a long time, the genetic basis of *INI1* loss was unknown, as only 1 allele was found to be deleted with no explanation of protein loss.[29] Recently, through next-generation sequencing, Calderaro and colleagues identified translocation of the second *INI1* allele as the hallmark of the disease.[30] Although these data need to be confirmed in a second independent cohort, the authors have pinpointed the importance of biallelic inactivation of *INI1* in these tumors.

Mucinous and Spindle Cell Carcinoma

For a long time, the biology of these tumors was unexplored. A recent report by Mehra and colleagues on 22 tumors identified the presence of either biallelic loss of the Hippo pathway and/or evidence of alteration of Hippo genes in 85% of samples.[31] The most frequent mutations were in *PTPN14* (31%) and *NF2* (22%), followed by mutations in other members of the pathway, such as the *SAV1* and *HIPK2* genes.[31] As a consequence, the majority of cases exhibited nuclear expression of YAP1, which is a readout of Hippo pathway inactivation.

Treatment Options for Non–Clear Cell Renal Cell Carcinoma

Given that ccRCC is the most common subtype of RCC, more data are available for the treatment of metastatic ccRCC than of nccRCC. However, multiple studies have reported on nccRCC; these consist of randomized clinical, prospective single-arm, and retrospective studies. We review below the relevant studies that address the treatment of nccRCC to provide a guide for patients and for the clinicians who treat RCC. First, we review prospective studies that included patients with all subtypes of nccRCC; then, we review the data available for each subtype of nccRCC, primarily via retrospective review, and data on immunotherapy.

Prospective Randomized Studies

There are 3 published randomized controlled studies that have included patients with nccRCC (Table 1). In 2014, Motzer and colleagues reported the first randomized study, RECORD-3 (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients With Metastatic Renal Cell Carcinoma), which included a cohort of patients with nccRCC and a larger cohort of patients with ccRCC.[32] This study was designed to compare sequential first-line everolimus (Afinitor, Novartis) and second-line sunitinib (Sutent, Pfizer) vs first-line sunitinib and second-line everolimus in patients with metastatic RCC. A total of 66 of 471 patients (14%) had nccRCC. The median first-line progression-free survival (PFS) in the nccRCC cohort was

Table 1. Summary of Prospective Randomized Studies in nccRCC

	Sunitinib	Everolimus
RECORD-3[32]		
N	35	31
Subtype	26 pRCC	24 pRCC
	7 chRCC	5 chRCC
	2 other	2 other
ORR, %	NA	NA
Median PFS, mo	7.2	5.1
Median OS, mo	NA	NA
ASPEN[33]		
N	51	57
Subtype	33 pRCC	37 pRCC
	10 chRCC	6 chRCC
	8 unclassified	14 unclassified
ORR, %	18	9
Median PFS, mo	8.3	5.6
Median OS, mo	31.5	13.2
ESPN[34]		
N	33	35
Subtype	14 pRCC	13 pRCC
	6 chRCC	6 chRCC
	3 tRCC	4 tRCC
	6 sarcomatoid	6 sarcomatoid
	4 unclassified	6 unclassified
ORR, %	9	3
Median PFS, mo	6.1	4.1
Median OS, mo	16.2	14.9

chRCC, chromophobe RCC; mo, months; N, number of patients; NA, not available; nccRCC, non–clear cell RCC; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pRCC, papillary RCC; RCC, renal cell carcinoma; tRCC, MiT family translocation RCC.

longer in the sunitinib arm than in the everolimus arm (7.2 months vs 5.1 months), but this difference was not statistically significant. Although the nccRCC cohort was relatively small, these were the first prospective data to suggest that that frontline anti-angiogenesis therapy in the form of sunitinib may provide a slight advantage in PFS vs an mTOR inhibitor.

The ASPEN (Afinitor [RAD001] vs. Sutent (Sunitinib) in Patients With Metastatic Non-Clear Cell Renal

Cell Carcinoma) phase 2 trial randomly assigned patients with metastatic nccRCC to everolimus or sunitinib.[33] Overall, 108 patients were randomly assigned to sunitinib (n=51) or everolimus (n=57), with a primary endpoint of PFS. The median PFS was longer in the patients treated with sunitinib than in those treated with everolimus (8.3 vs 5.6 months; hazard ratio, 1.41 [80% CI, 1.03-1.92]; P=.16). Sunitinib resulted in an improved median PFS for patients with good-risk disease (14.0 vs 5.7 months) and intermediate-risk disease (6.5 vs 4.9 months) by Memorial Sloan Kettering Cancer Center (MSKCC) score. However, patients with poor-risk disease had a longer median PFS with everolimus than with sunitinib (6.1 vs 4.0 months). Interestingly, outcomes in the subset of patients who had chromophobe histology were better in those who were treated with everolimus than in those who were treated with sunitinib, in terms of both response rate (33% vs 10%) and median PFS (11.4 vs 5.5 months). Despite an improved objective response rate (ORR) and PFS in the sunitinib arm, the difference in overall survival (OS) between the 2 treatment groups was not statistically significantly different, with a median OS of 13.2 months in the everolimus group and of 31.5 months in the sunitinib group (P=.60); this finding was likely related to the use of second-line therapies (approximately 64% of patients received subsequent therapy). These results parallel those of RECORD-3, in which the authors demonstrated that first-line sunitinib yielded a longer PFS compared with everolimus; however, the improvement in PFS did not translate into improvement in OS in either study, suggesting that second-line therapies may affect OS. In ASPEN, it is interesting that patients with chromophobe histology (n=16) had better ORR and PFS with everolimus (n=6) than with sunitinib (n=10). However, given the relatively small number of patients and the fact that MSKCC prognostic risk grouping was not provided in this small subset, we believe it is difficult to draw the conclusion that everolimus improved outcomes in comparison with sunitinib in this small subset.

Finally, the ESPN trial (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non–Clear Cell Renal Cell Carcinoma), which allowed a crossover after disease progression with the first-line agent, sought to determine the relative efficacy of everolimus vs sunitinib in the first-line setting in nccRCC, with a primary endpoint of PFS in the first-line setting.[34] A total of 68 patients were evaluable for treatment outcomes. The ORR in both groups was low (9% in the sunitinib arm and 3% in the everolimus arm). Although the median PFS was numerically longer in the sunitinib arm (6.1 vs 4.1 months), this difference was not statistically significant (P=.6). Similarly, the median OS was numerically

longer in the sunitinib arm, but the difference was not statistically significant (16.2 vs 14.9 months; P=.18).

Prospective Single-Arm Studies

In addition to the 3 prospective randomized studies involving patients with nccRCC, 7 prospective, single-arm studies have been conducted in patients with nccRCC (summarized in Table 2). These include 3 studies with single-agent sunitinib,[35-37] 1 study with single-agent everolimus,[38] 1 study with the combination of everolimus and bevacizumab (Avastin, Genentech),[39] and 2 studies with cytotoxic chemotherapy.[40,41]

The 3 single-arm studies assessing sunitinib included patients with a variety of nccRCC subtypes; papillary RCC was the histologic subtype most frequently studied. The ORR was approximately 5% in the trials of Molina and colleagues and Tannir and colleagues, whereas the ORR was 36% in the Korean phase 2 trial by Lee and colleagues.[35-37] In the subset of 5 patients with chromophobe histology, Tannir and colleagues observed 2 partial responders and a median PFS of 12.7 months.[36] Conversely, the median PFS in the subset of patients with papillary histology (n=27) was shorter than that of the group as a whole. This is consistent with the trial of Molina and colleagues, in which no objective responses were found in the patients with papillary RCC.[35] The median PFS times in these 3 studies were 5.5, 2.7, and 6.4 months, suggesting that sunitinib has a modest clinical activity in metastatic nccRCC compared with its activity in ccRCC.

Koh and colleagues reported a modest clinical activity with everolimus, which yielded an ORR of 10.2% and a median PFS of 5.2 months.[38] In the 8 patients with chromophobe histology, the ORR was 25%, and the PFS was longer than it was in patients with the other nccRCC subtypes (P=.084), with the caveat that these subgroups included very small numbers of patients.

In a study reported by Voss and colleagues of 35 patients with advanced nccRCC, the combination of everolimus plus bevacizumab produced an ORR of 29%, a median PFS of 11 months, and a median OS of 18.5 months.[39] Interestingly, patients with either papillary histology or unclassified histology with papillary features (n=19) had improved clinical outcomes, with an ORR of 43%, a median PFS of 12.9 months, and a median OS of 28.2 months. In an exploratory genomic analysis, the authors identified that 5 (36%) of 14 patients with a major papillary component harbored somatic mutations in *ARID1A*, and all 5 patients derived treatment benefit. The caveat of cross-trial comparisons notwithstanding, the clinical activity of bevacizumab and everolimus in this cohort of patients with nccRCC was quite impressive, with improved ORR and PFS in comparison with other prospective trials. The improved outcome in the subset

Table 2. Summary of Prospective Single-Arm Studies in nccRCC

Agent(s)/Authors	N	Subtypes	ORR, %	Median PFS, mo	Median OS, mo
Sunitinib					
Molina et al[35]	23	8 pRCC	4	5.5	NA
		15 other			
Tannir et al[36]	57	27 pRCC	5	2.7	16.8
		5 chRCC			
		6 CDC/RMC			
		7 sarcomatoid			
		4 other			
		8 unclassified			
Lee et al[37]	31	22 pRCC	36	6.4	25.6
		3 chRCC			
		1 tRCC			
		5 unclassified			
Everolimus					
Koh et al[38]	49	29 pRCC	10.2	5.2	NA
		8 chRCC			
		2 CDC			
		4 sarcomatoid			
		6 unclassified			
Bevacizumab Plus Everolimus					
Voss et al[39]	35	5 pRCC	29	11.0	18.5
		5 chRCC			
		2 RMC			
		23 unclassified			
Chemotherapy					
Capecitabine	51	39 pRCC	26	10.1	18.3
(Tsimafeyey et al)[40]		7 chRCC			
		5 CDC			
Pemetrexed plus gemcitabine	14	5 pRCC	0	3.2	23.2
(Richey et al)[41]		2 chRCC			
		3 CDC			
		2 tRCC			
		2 unclassified			

CDC, collecting duct carcinoma; chRCC, chromophobe RCC; mo, months; N, number of patients; nccRCC, non–clear cell RCC; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pRCC, papillary RCC; RCC, renal cell carcinoma; RMC, renal medullary carcinoma; tRCC, MiT family translocation RCC.

of patients with papillary RCC or unclassified RCC with papillary features is intriguing and warrants follow-up. Finally, the association of *ARID1A* mutations with clinical benefit also deserves further evaluation.

The 2 studies investigating cytotoxic chemotherapy in this setting were designed with single-agent capecitabine and a combination of pemetrexed (Alimta, Lilly) and gemcitabine.[40,41] The primary endpoint in each study was ORR. In the first trial, a total of 51 patients received capecitabine, producing an ORR of 26%, a median PFS of 10.1 months, and a median OS of 18.3 months. The majority of patients had papillary histology (76%) and an MSKCC intermediate-risk prognosis (86%). Given the rather significant clinical activity, the authors proposed an additional prospective randomized trial comparing capecitabine with a control or placebo arm.[40] In the second trial, however, in which 14 patients received a combination of pemetrexed and gemcitabine, no patients showed an objective response, and the median PFS was only 3.2 months.[41] Owing to its relatively high level of toxicity and poor efficacy, the authors concluded that this regimen does not warrant further study.

Disease-Specific Studies

In addition to the randomized and prospective studies previously discussed, multiple retrospective studies are assessing the efficacy of various agents in nccRCC, and most of these studies confirm the experience of the randomized and prospective studies.[42-47] Here, we focus on the retrospective studies that are specific to nccRCC subtypes, for which randomized and prospective data are limited.

Papillary RCC. In addition to prospective studies that have grouped all patients with nccRCC together, there are multiple prospective studies that are specific to papillary RCC. These include evaluation of chemotherapy (combination of carboplatin and paclitaxel),[48] dual c-MET/ vascular endothelial growth factor receptor (VEGFR) inhibition (foretinib),[49] epidermal growth factor receptor (EGFR) inhibition (erlotinib; Tarceva, Genentech/Astellas),[50] sunitinib,[51] and everolimus.[52] Although none of the patients treated with chemotherapy showed an objective response, the rates of response to targeted agents varied between 11% and 13.5% (summarized in Table 3).

As discussed earlier, activating mutations or amplifications in *MET* provide the rationale for testing foretinib in this cohort. In the foretinib phase 2 trial, 2 different dosing regimens were used, and patients were stratified by the presence or absence of MET pathway activation. In total, 74 patients were enrolled, 37 patients in each dosing cohort. The ORR was 13.5% and the median PFS was 9.3 months. The ORR in patients with germline *MET*

Table 3. Summary of Prospective Studies in Papillary RCC

Agent(s)/ Authors	N	ORR, %	Median PFS, mo	Median OS, mo
Carboplatin and paclitaxel				
Bylow et al[48]	16	0	NA	NA
Foretinib				
Choueiri et al[49]	74	13.5	9.3	NA
Erlotinib				
Gordon et al[50]	45	11	NA	27
Sunitinib				
Ravaud et al[51]	61			
	15 type 1	13	6.6	17.8
	46 type 2	11	5.5	12.4
Everolimus				
Escudier et al[52]	69			
	23 type 1	NA	7.9	28.0
	46 type 2	NA	5.1	24.2

mo, months; N, number of patients; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

mutations was 50%, but it was only 9% in those with sporadic mutations, suggesting germline c-*MET* mutation as a possible biomarker.[43] Trials with tyrosine kinase inhibitors (TKIs), such as cabozantinib (Cabometyx, Exelixis) and savolitinib, both of which target MET, are actively recruiting patients with papillary RCC.[53]

Ravaud and colleagues reported on the phase 2 trial activity of sunitinib in 15 patients with type 1 papillary RCC and 46 patients with type 2 papillary RCC.[51] In patients with type 1 disease, the ORR was 13%, the median PFS was 6.6 months, and the median OS was 17.8 months. In patients with type 2 disease, the ORR was 11%, the median PFS was 5.5 months, and the median OS was 12.4 months. In the everolimus study by Escudier and colleagues, patients with type 1 papillary histology had a median PFS of 7.9 months and a median OS of 28.0 months. Those with papillary type 2 histology had a median PFS of 5.1 months and a median OS of 24.2 months.[52]

Collecting Duct Carcinoma. Because of its rarity, little information exists on the clinical efficacy of agents for patients with collecting duct carcinomas. Below, we review 2 prospective studies and 1 retrospective review. In 2007, Oudard and colleagues published a prospective phase 2 study of gemcitabine and platinum in patients

with metastatic collecting duct carcinoma.[55] A total of 23 patients were treated. The ORR was 26%, the median PFS was 7.1 months, and the median OS was 10.5 months. In 2013, Pecuchet and colleagues published a case series involving 5 patients with metastatic collecting duct carcinoma treated with the combination of bevacizumab, gemcitabine, and a platinum agent.[56] In this study, the ORR was 60%, the median PFS was 15.1 months, and the median OS was 27.8 months. The authors attributed the clinical benefit in these patients to the addition of bevacizumab to the gemcitabine/platinum combination. Zhao and colleagues published a case report and a review of the literature on patients with metastatic collecting duct carcinoma treated with various targeted agents.[57] In the case report, the authors reported on 1 patient who had achieved a partial remission with sorafenib (Nexavar, Bayer). In their review of the literature, the authors identified 12 patients with metastatic collecting duct tumors who were treated with targeted agents (6 with sorafenib, 4 with sunitinib, and 2 with temsirolimus [Torisel, Pfizer]), and they concluded that 33% of these patients had derived clinical benefit from these therapies.

Chromophobe RCC. Owing to the rarity of this tumor subtype, there are no studies specifically dedicated to patients with chromophobe histology. In a retrospective review, Choueiri and colleagues described the experience of treating 12 patients with metastatic chromophobe RCC with anti-VEGF regimens. Of the 12 patients with chromophobe RCC, 3 (25%) exhibited a response (2 patients treated with sorafenib and 1 patient treated with sunitinib), and the median PFS was 10.6 months.[42]

Renal Medullary Carcinoma. There are no published prospective studies specifically dedicated to patients with medullary histology. In 2007, Hakimi and colleagues retrospectively described their experience with 9 patients who had metastatic medullary carcinoma.[58] All 9 patients had sickle cell trait, and 8 patients had a right-sided mass. In this study, 7 of the 9 patients underwent radical nephrectomy with varying neoadjuvant therapies used. The OS ranged from 4 to 16 months, with only 2 patients alive at the last follow-up visit. Given the short OS in this cohort, the authors concluded that surgery alone is inadequate in the management of patients with renal medullary carcinoma.

In 2013, Maroja Silvino and colleagues described their experience in the treatment of 5 patients with medullary carcinoma from a referral center in Brazil.[59] All 5 patients had sickle cell trait, 4 were male, and 3 had a diagnosis of metastatic disease. All 5 patients were treated with platinum-based chemotherapy, and 2 patients had a partial response with gemcitabine and cisplatin.

Recently, the outcomes of 52 patients with renal medullary carcinoma were reported through a multi-center collaborative study.[60] The outcomes were poor, with a median OS of 13.0 months. However, subgroup analysis showed that the median OS was better in the patients who underwent nephrectomy than in those who did not (16.4 vs 7.0 months; *P*<.001). Of note, in the 28 patients who received targeted therapies, no objective responses were observed. Thus, the mainstay of systemic therapy is combination cytotoxic chemotherapy, but renal medullary carcinoma remains a very difficult disease to treat, with little evidence to guide treatment regimens.

Translocation RCC. There are no prospective studies specifically dedicated to patients with translocation RCC. In 2010, through the Juvenile RCC Network, a French group examined the clinical activity of anti-VEGF agents or mTOR inhibitors in 21 patients with translocation RCC.[61] The ORR in this study was 33%, and the median OS of the entire cohort was 27 months. In patients who received sunitinib as first-line therapy (n=11), the median PFS was 8.2 months. A partial response occurred in 1 patient receiving an mTOR inhibitor, and 6 patients had stable disease. In 2010, Choueiri and colleagues performed a retrospective evaluation of the efficacy of anti-VEGF targeted therapy in a total of 15 US patients.[62] In this cohort, 10, 3, and 2 patients received sunitinib, sorafenib, and monoclonal anti-VEGF antibodies, respectively. The ORR was 20%, and the median PFS and OS were 7.1 months and 14.3 months, respectively.

Immunotherapy
There is a paucity of data regarding the efficacy of immunotherapy in nccRCC. We review the interleukin 2 (IL-2) and anti–programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) experience below.

Interleukin 2. The US Food and Drug Administration approved high-dose IL-2 in 1992, on the basis of its ability to produce durable responses in a small percentage of patients with mRCC.[63] In these early trials, high-dose IL-2 achieved an ORR of 14% in 255 patients; however, the vast majority of these patients had ccRCC, making it difficult to draw conclusions about patients with nccRCC. In a small retrospective study, Upton and colleagues reviewed outcomes of 10 patients with nccRCC and found no responders, with a median OS of less than 1 year.[64] On the basis of these data and other expert investigator experience, patients with nccRCC are not considered good candidates for treatment with high-dose IL-2.

Programmed Death 1/Programmed Death Ligand 1. At present, no data from clinical studies on the efficacy

of anti–PD-1 or anti–PD-L1 agents in patients with nccRCC are available. However, there is at least a rationale and an unmet need for these studies. Choueiri and colleagues assessed PD-L1 expression in 101 nccRCC tumors and found that 11% of the tumors were positive for PD-L1 by their cutoff.[65] In a separate study, investigators at the Mayo Clinic assessed PD-L1 expression in 26 patients with sarcomatoid RCC and found PD-L1 expression in 50% of tumors; they also described 1 patient with sarcomatoid RCC who responded to anti–PD-1 therapy.[66] Future studies will investigate the clinical efficacy of anti–PD-1/PD-L1; several ongoing trials are currently evaluating the immuno-oncologic agents nivolumab (Opdivo, Bristol-Myers Squibb), ipilimumab (Yervoy, Bristol-Myers Squibb) in combination with nivolumab, pembrolizumab (Keytruda, Merck), and atezolizumab (Tecentriq, Genentech) in nccRCC.[67]

Clinical Summary and Future Perspectives

Owing to the development of many promising novel agents and adequately powered clinical trials, the treatment landscape of ccRCC is rapidly evolving and clinical outcomes are improving. Unfortunately, advances in the treatment landscape of metastatic nccRCC have been slow, mainly because the rarity of each subtype makes it difficult to test the efficacy of novel agents robustly in clinical studies. However, we now have cumulative data about the limited utility of the anti-VEGF agents and mTOR inhibitors in nccRCC, allowing us at least to provide patients with adequate information and expectations. Insights into genomics and epigenetics, and advances in immunology and immunotherapy, allow us to be optimistic that therapeutic gains will be made in the near future against these variant RCC subtypes.

Disclosures

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer.* 2013;49(6):1374-1403.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.

3. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs-part A: renal, penile, and testicular tumours. *Eur Urol.* 2016;70(1):93-105.

4. Cheval L, Pierrat F, Rajerison R, Piquemal D, Doucet A. Of mice and men: divergence of gene expression patterns in kidney. *PLoS One.* 2012;7(10):e46876.

5. Malouf GG, Su X, Zhang J, et al. DNA methylation signature reveals cell ontogeny of renal cell carcinomas. *Clin Cancer Res.* 2016;22(24):6236-6246.

6. Davis CF, Ricketts CJ, Wang M, et al; Cancer Genome Atlas Research Network. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell.* 2014;26(3):319-330.

7. Malouf GG, Compérat E, Yao H, et al. Unique transcriptomic profile of collecting duct carcinomas relative to upper tract urothelial carcinomas and other kidney carcinomas. *Sci Rep.* 2016;6:30988.

8. Malouf GG, Ali SM, Wang K, et al. Genomic characterization of renal cell carcinoma with sarcomatoid dedifferentiation pinpoints recurrent genomic alterations. *Eur Urol.* 2016;70(2):348-357.

9. Chen F, Zhang Y, Şenbabaoğlu Y, et al. Multilevel genomics-based taxonomy of renal cell carcinoma. *Cell Rep.* 2016;14(10):2476-2489.

10. Leroy X, Zini L, Leteurtre E, et al. Morphologic subtyping of papillary renal cell carcinoma: correlation with prognosis and differential expression of MUC1 between the two subtypes. *Mod Pathol.* 2002;15(11):1126-1130.

11. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. *Nat Genet.* 1997;16(1):68-73.

12. Lubensky IA, Schmidt L, Zhuang Z, et al. Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. *Am J Pathol.* 1999;155(2):517-526.

13. Albiges L, Guegan J, Le Formal A, et al. MET is a potential target across all papillary renal cell carcinomas: result from a large molecular study of pRCC with CGH array and matching gene expression array. *Clin Cancer Res.* 2014;20(13):3411-3421.

14. Tomlinson IP, Alam NA, Rowan AJ, et al; Multiple Leiomyoma Consortium. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat Genet.* 2002;30(4):406-410.

15. Linehan WM, Spellman PT, Ricketts CJ, et al; Cancer Genome Atlas Research Network. Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med.* 2016;374(2):135-145.

16. Volpe A, Novara G, Antonelli A, et al; Surveillance and Treatment Update on Renal Neoplasms (SATURN) Project; Leading Urological No-Profit Foundation for Advanced Research (LUNA) Foundation. Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. *BJU Int.* 2012;110(1):76-83.

17. Vocke CD, Yang Y, Pavlovich CP, et al. High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dubé-associated renal tumors. *J Natl Cancer Inst.* 2005;97(12):931-935.

18. Shuch B, Ricketts CJ, Vocke CD, et al. Germline PTEN mutation Cowden syndrome: an underappreciated form of hereditary kidney cancer. *J Urol.* 2013;190(6):1990-1998.

19. Komai Y, Fujiwara M, Fujii Y, et al. Adult Xp11 translocation renal cell carcinoma diagnosed by cytogenetics and immunohistochemistry. *Clin Cancer Res.* 2009;15(4):1170-1176.

20. Kauffman EC, Ricketts CJ, Rais-Bahrami S, et al. Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. *Nat Rev Urol.* 2014;11(8):465-475.

21. Malouf GG, Su X, Yao H, et al. Next-generation sequencing of translocation renal cell carcinoma reveals novel RNA splicing partners and frequent mutations of chromatin-remodeling genes. *Clin Cancer Res.* 2014;20(15):4129-4140.

22. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature.* 2013;499(7456):43-49.

23. Durinck S, Stawiski EW, Pavía-Jiménez A, et al. Spectrum of diverse genomic alterations define non-clear cell renal carcinoma subtypes. *Nat Genet.* 2015;47(1):13-21.

24. Malouf GG, Monzon FA, Couturier J, et al. Genomic heterogeneity of translocation renal cell carcinoma. *Clin Cancer Res.* 2013;19(17):4673-4684.

25. Wang J, Papanicolau-Sengos A, Chintala S, et al. Collecting duct carcinoma of the kidney is associated with CDKN2A deletion and SLC family gene up-regulation. *Oncotarget.* 2016;7(21):29901-29915.

26. Pal SK, Choueiri TK, Wang K, et al. Characterization of clinical cases of collecting duct carcinoma of the kidney assessed by comprehensive genomic profiling.

Eur Urol. 2016;70(3):516-521.

27. Anazoeze M, Najibah G, Garba U, et al. Is renal medullary carcinoma the seventh nephropathy in sickle cell disease? A multi-center Nigerian survey. *Afr Health Sci.* 2016;16(2):490-496.

28. Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature.* 2011;469(7331):539-542.

29. Calderaro J, Moroch J, Pierron G, et al. SMARCB1/INI1 inactivation in renal medullary carcinoma. *Histopathology.* 2012;61(3):428-435.

30. Calderaro J, Masliah-Planchon J, Richer W, et al. Balanced translocations disrupting SMARCB1 are hallmark recurrent genetic alterations in renal medullary carcinomas. *Eur Urol.* 2016;69(6):1055-1061.

31. Mehra R, Vats P, Cieslik M, et al. Biallelic alteration and dysregulation of the Hippo pathway in mucinous tubular and spindle cell carcinoma of the kidney. *Cancer Discov.* 2016;6(11):1258-1266.

32. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2014;32(25):2765-2772.

33. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol.* 2016;17(3):378-388.

34. Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. *Eur Urol.* 2016;69(5):866-874.

35. Molina AM, Feldman DR, Ginsberg MS, et al. Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma. *Invest New Drugs.* 2012;30(1):335-340.36. Tannir NM, Plimack E, Ng C, et al. A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol.* 2012;62(6):1013-1019.

37. Lee JL, Ahn JH, Lim HY, et al. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. *Ann Oncol.* 2012;23(8):2108-2114.

38. Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. *Ann Oncol.* 2013;24(4):1026-1031.

39. Voss MH, Molina AM, Chen YB, et al. Phase II and correlative genomic analysis of everolimus plus bevacizumab in advanced non-clear cell renal cell carcinoma. *J Clin Oncol.* 2016;JCO679084.

40. Tsimafeyeu I, Demidov L, Kharkevich G, et al. Phase II, multicenter, uncontrolled trial of single-agent capecitabine in patients with non-clear cell metastatic renal cell carcinoma. *Am J Clin Oncol.* 2012;35(3):251-254.

41. Richey SL, Tamboli P, Ng CS, et al. Phase II trial of pemetrexed plus gemcitabine in patients with locally advanced and metastatic nonclear cell renal cell carcinoma. *Am J Clin Oncol.* 2013;36(5):450-454.

42. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol.* 2008;26(1):127-131.

43. Paglino C, Imarisio I, Ganini C, et al. Sunitinib in advanced metastatic non-clear cell renal cell carcinoma: a single institution retrospective study. *Future Oncol.* 2012;8(12):1605-1612.

44. Stadler WM, Figlin RA, McDermott DF, et al; ARCCS Study Investigators. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer.* 2010;116(5):1272-1280.

45. Voss MH, Bastos DA, Karlo CA, et al. Treatment outcome with mTOR inhibitors for metastatic renal cell carcinoma with nonclear and sarcomatoid histologies. *Ann Oncol.* 2014;25(3):663-668.

46. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol.* 2009;26(2):202-209.

47. Vera-Badillo FE, Templeton AJ, Duran I, et al. Systemic therapy for non-clear cell renal cell carcinomas: a systematic review and meta-analysis. *Eur Urol.* 2015;67(4):740-749.

48. Bylow KA, Atkins MB, Posadas EM, Stadler WM, McDermott DF. Phase II trial of carboplatin and paclitaxel in papillary renal cell carcinoma. *Clin Genitourin Cancer.* 2009;7(1):39-42.

49. Choueiri TK, Vaishampayan U, Rosenberg JE, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. *J Clin Oncol.* 2013;31(2):181-186.

50. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. *J Clin Oncol.* 2009;27(34):5788-5793.

51. Ravaud A, Oudard S, De Fromont M, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG). *Ann Oncol.* 2015;26(6):1123-1128.

52. Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer.* 2016;69:226-235.

53. Clinicaltrials.gov. Cabozantinib-S-malate, crizotinib, volitinib, or sunitinib malate in treating patients with locally advanced or metastatic kidney cancer. https://clinicaltrials.gov/ct2/show/NCT02761057?term=savolitinib+papillary+renal+cell+carcinoma&rank=2. Identifier: NCT02761057. Accessed February 28, 2017.

54. Escudier BJ, Bracarda S, Maroto Rey JP, et al. Open-label, phase II raptor study of everolimus (EVE) for papillary mRCC: efficacy in type 1 and type 2 histology [ASCO abstract 410]. *J Clin Oncol.* 2014;32(4)(suppl).

55. Oudard S, Banu E, Vieillefond A, et al; GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales). Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales) study. *J Urol.* 2007;177(5):1698-1702.

56. Pécuchet N, Bigot F, Gachet J, et al. Triple combination of bevacizumab, gemcitabine and platinum salt in metastatic collecting duct carcinoma. *Ann Oncol.* 2013;24(12):2963-2967.

57. Zhao RN, Nie LH, Gong R, et al. Active targeted therapy for metastatic collecting duct carcinoma of the kidney: a case report and review of the literature. *Int Urol Nephrol.* 2013;45(4):1017-1021.

58. Hakimi AA, Koi PT, Milhoua PM, et al. Renal medullary carcinoma: the Bronx experience. *Urology.* 2007;70(5):878-882.

59. Maroja Silvino MC, Venchiarutti Moniz CM, Munhoz Piotto GH, Siqueira S, Galapo Kann A, Dzik C. Renal medullary carcinoma response to chemotherapy: a referral center experience in Brazil. *Rare Tumors.* 2013;5(3):e44.

60. Shah AY, Karam JA, Malouf GG, et al. Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study. *BJU Int.* 2016.

61. Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. *Ann Oncol.* 2010;21(9):1834-1838.

62. Choueiri TK, Lim ZD, Hirsch MS, et al. Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic Xp11.2 translocation renal cell carcinoma. *Cancer.* 2010;116(22):5219-5225.

63. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol.* 1995;13(3):688-696.

64. Upton MP, Parker RA, Youmans A, McDermott DF, Atkins MB. Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy. *J Immunother.* 2005;28(5):488-495.

65. Choueiri TK, Fay AP, Gray KP, et al. PD-L1 expression in nonclear-cell renal cell carcinoma. *Ann Oncol.* 2014;25(11):2178-2184.

66. Joseph RW, Millis SZ, Carballido EM, et al. PD-1 and PD-L1 expression in renal cell carcinoma with sarcomatoid differentiation. *Cancer Immunol Res.* 2015;3(12):1303-1307.

67. Clinicaltrials.gov. Study of pembrolizumab (MK-3475) monotherapy in locally advanced/metastatic renal cell carcinoma (MK-3475-427/KEYNOTE-427). Identifier: NCT02853344. Accessed February 28, 2017.