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Recommendations for the Management of Rare Kidney Cancers

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Abstract

Context: The European Association of Urology Renal Cell Carcinoma Guideline Panel recently conducted a systematic review of treatment options for patients with advanced non–clear-cell renal cell carcinomas (RCCs), which showed a substantial lack of evidence for management recommendations.
Objective: To improve the outcomes of patients with rare kidney cancers (RKCs), we performed a subsequent unstructured review to determine current treatment strategies and druggable pathways, involving key stakeholders with a global perspective to generate recommendations.
Evidence acquisition: Based on the systematic review, literature was queried in Pubmed, Medline, and abstracts from proceedings of European Society for Medical Oncology and American Society of Clinical Oncology, in addition to consulting key opinion leaders and stakeholders. A conventional narrative review strategy was adopted to summarize the data.
Evidence synthesis: The systematic review showed an absence of evidence for treating RKCs, with data only supporting sunitinib or MET inhibitors for some specific subtypes. However, a growing body of evidence implicates druggable pathways in specific RKC subtypes. To test hypotheses, the small patient numbers in each subtype require coordinated multicenter efforts. Many RKC patients are currently excluded from studies or are not analyzed using subtype-specific parameters, despite their unmet medical need.
Conclusions: We recognize the need for additional multicenter studies and subtype-specific analyses; however, we present management recommendations based on the data available. Web-based tools facilitating subtype-specific global registries and shared translational research resources will help generate sufficient data to formulate evidence-based recommendations for guidelines.

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Patient summary: Patients confronted with rare kidney cancers are often treated the same way as clear-cell renal cell carcinoma patients, despite little evidence from randomized trials. Molecular characterization of tumors to stratify patients may improve outcomes. Availability of potential agents and trials remain a problem. Collaboration among medical centers is important to pool scarce data.

1. Introduction

Renal cell carcinoma (RCC) is a relatively rare cancer, although it is estimated that there are >338 000 new cases annually, with a 22% increase projected by 2020 [1]. RCC is characterized by distinct histological subtypes defined by the 2016 World Health Organization classification [2]. Among the malignant tumors, clear-cell RCC (ccRCC) accounts for approximately 75% of kidney cancer. Subtypes making up the remaining 20–25% RCCs are papillary types (pRCC) 1 and 2, chromophobe (chRCC), collecting duct, translocation, medullary, and other very rare RCCs; collectively, these variants of kidney cancer are often termed "non-ccRCCs". Like ccRCCs, these entities may be hereditary or sporadic [3]; however, unlike ccRCCs, limited data are available for evidence-based treatment management, largely due to a lack of trials specific to this population. As "non-ccRCC" is a nondesignation, we employ the inclusive nomenclature "rare kidney cancers" (RKCs).

The European Association of Urology (EAU) RCC Guideline Panel recently performed a systematic review of management strategies for "non-ccRCCs" [4]. The outcome of this process revealed an almost complete lack of evidence. In response to this systematic review, the authors of this paper met in San Francisco, USA, to reach a consensus on "how to improve outcomes for 'rare kidney cancer' patients as a global effort." Specialists (urologists, medical oncologists, and nephrologists) focused on the care of patients with RKCs, as well as patient advocates and two RKC survivors, unanimously agreed on the urgent need for improved medical management of RKCs. This paper is a call to action to appreciate the burden of RKCs and move forward with a roadmap to improve the outcome for these patients with well-coordinated clinical trials and translational research efforts.

2. Evidence acquisition

In addition to the search results derived from the systematic review, we queried the relevant literature in Pubmed, Medline, abstracts from proceedings of European Society for Medical Oncology, and American Society of Clinical Oncology(-GU) until February 18, 2017, in addition to consulting key opinion leaders and stakeholders. A conventional narrative review strategy was adopted to summarize the data, available online (Appendices A and B).

3. Evidence synthesis

The evidence for systemic treatment of metastatic non-ccRCC shows a trend toward favoring vascular endothelial growth factor (VEGF) pathway–targeted therapy over inhibitors of the mammalian target of rapamycin (mTOR), although statistical significance was not reached [4]. The lack of strong evidence calls for experimental data and recommendations from experts in the field of RKCs as well as key stakeholders to help generate informed management strategies [5].

3.1. Definition of RKCs

RKCs comprise a broad spectrum of over a dozen histopathological entities [2]. Papillary RCCs (pRCC types 1 and 2) and chRCCs are more common than the other RKCs. Distinguishing genomic characteristics help characterize RKCs (Supplementary Tables 1 and 2). An estimated 5–8% of RCCs have a strong hereditary component, and 13 distinct hereditary RCC syndromes are known, each associated with specific germline mutations, RCC histology, and nonrenal manifestations [6]: von Hippel–Lindau syndrome (VHL; MIM193300), hereditary pRCC (MIM605074), Birt–Hogg–Dubé (BHD; MIM135150) syndrome, hereditary leiomyomatosis and renal cell cancer (HLRCC; MIM150800), tuberous sclerosis (TS; MIM191100), germline succinate dehydrogenase (SDH) mutations, hyperparathyroidism–jaw tumor syndrome (MIM145001), phosphatase and tensin homolog (PTEN) hamartoma syndrome (MIM601728), constitutional chromosome 3 translocation (MIM144700), *BAP1* hereditary cancer predisposition syndrome (MIM614327), and *MITF*-associated susceptibility to melanoma and RCC syndrome (MIM614456). The current best practice is to consider genetic counseling for individuals suspected of having a hereditary predisposition including early age of onset (age <46 yr), since timely diagnosis could prevent or identify comorbidities at an early stage [7]. Somatic fusion translocations of *TFE3* and *TFEB* may affect 15% of patients with RCC <45 yr and 20–45% of children and young adults with RCC (MIM300854). Even though some hereditary RCC syndromes, such as VHL, predispose to ccRCC and not to one of the RKC subtypes, all hereditary RCC syndromes should be considered as RKCs since they typically require specialized care.

3.2. Current treatment options

Cytoreductive nephrectomy should be considered carefully in RKC patients, with the exception of pRCC type 1, where it is considered beneficial [8]. In the metastatic setting, limited available data suggest that RKCs are less responsive to single-agent VEGF pathway–targeted therapy or mTOR inhibitors than ccRCCs (Table 1). In a retrospective study including 252 patients with RKCs and 1963 patients with ccRCCs treated with targeted therapies, the median overall

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Table 1 – Randomized and single-arm phase 2 trials that reported outcome for various RKC subtypes

Trial [Reference]	Patient (*n*)	Subtypes (*n*)	Treatment/ comparator	Line	PFS (mo):[95% CI], (HR [95% CI])	OS (mo) [95% CI], (HR [95% CI])	RECIST response		ORR (%)
Randomized controlled trials									
ASPEN NCT01108445 [13]	108	pRCC 76/108 chRCC 16/108 uRCC	Everolimus (EVE) versus sunitinib (SUN)	First	EVE: 5.6 [5.5–60] SUN: 8.3 [5.8–11.4] [a] (1.41 [0.88–2.27])	EVE: 13.2 [9.7–37.9] SUN: 31.5 [14.8–NA] (1.12 [0.7–2])	EVE: CR: 1 PR: 4 SD: 30 PD: 13	SUN: CR: 0 PR: 9 SD: 30 PD: 10	EVE: 9% SUN: 18%
ESPN NCT01185366 [12]	68	pRCC 27/68 chRCC 12/68 TRCC uRCC Sarcomatoid	Everolimus (EVE) versus sunitinib (SUN)	First, second	EVE: 4.1 [2.7–10.5] SUN: 6.1[4.2–9.4] (1.16 [0.67–2.01])	EVE: 14.9 [8.0–23.4] SUN: 16.2 [14.2–NA] (NA)	EVE: CR: 0 PR: 1 SD: 24 PD: 8	SUN: CR: 0 PR: 3 SD: 21 PD: 9	EVE: 3% SUN: 11%
RECORD3 NCT00903175 [14]	66 [b]	pRCC 50/66 chRCC 12/66 uRCC	Everolimus (EVE) versus sunitinib (SUN)	First, second	EVE: 5.1 [2.6–7.9] SUN: 7.2 [5.4–13.8] (1.5 [0.9–2.8])	NA	NA	NA	NA
SWOG1107 NCT01688973 [4]	50	pRCC 50/50	Tivantinib (TIV) versus tivantinib + erlotinib (ERL)	First, second	TIV: 2 [NA] TIV + ERL: 5.4 [NA] (NA)	TIV: 10.3 [NA] TIV + ERL: 11.3 [NA] (NA)	NA	NA	TIV: 0 TIV + ERL: 0
ARCC NCT00065468 [4]	73 [b]	pRCC 55/73 uRCC	IFN-a versus temsirolimus (TEM)	First	IFN-a: 1.8 [1.6–2.1] TEM: 7 [3.9–8.9] (0.38 [0.23–0.62])	IFN-a: 4.3 [3.2–7.3] TEM: 11.6 [8.9–13] (0.49 [0.29–0.85])	NA		IFN-a: 12% TEM: 12%
Single-arm studies									
RAPTOR NCT00688753 [11]	88 ITT/ 92	pRCC type 1 14/88 pRCC type 2 43/88	Everolimus	First	Type 1: 7.9 [2.1–11.0] Type 2: 5.1 [3.3–5.5] (NA)	Type 1: 28.0 [7.6–NA] Type 2: 24.2 [15.8–32.8] (NA)	ITT: CR: 0 PR: 1 SD: 57 PD: 28		ITT:1%
SUPAP NCT00541008 [15]	61	pRCC type 1 15/61 pRCC type 2 46/61	Sunitinib	First	Type 1: 6.6 [2.8–14.8] Type 2: 5.5 [3.8–7.1]	Type 1: 17.8 [5.7–26.1] Type 2: 12.4 [8.4–14.3]	Type 1/2 CR: 0/0 PR: 2/5 SD: 10/25 PD: 3/16		NA
NCT01399918 [35]	35	pRCC 5/35 chRCC 5/35 RMC 2/35 uRCC 23/35 p-uRCC 14 uRCC 9	Bevacizumab + everolimus	First	All: 11.0 [3.8–19.3] p-uRCC: 12.9 [10.9–NA] uRCC: 1.9 [1.6–NA]	All: NA p-uRCC: 28.9 [NA] uRCC: 9.3 [NA]	All: CR: 1 PR: 9 SD: 15 PD: 8		All: 29% p-uRCC: 43% uRCC: 11%
NCT00726323 [31]	74	pRCC any type	Foretinib	First, second	9.3 [6.9–12.9]	Not reached	CR: 0 PR: 10 SD: 61 PD: 3		13.5%
NCT00422019 [29]	61	ccRCC 46/61 pRCC 7/61 chRCC 3/61 uRCC 5/61	AMG102	First, second, third	3.7 [1.8–7.6]	14.9 [9.4–NA]	CR: 0 PR: 1 SD: 26 PD: 16 NA: 18		2.5%
NCT02127710 [33]	109	pRCC any type MET+ 44/109 MET– 46/109 NA 19/109	Savolitinib	First	MET+: 6.2 [4.1–7.0] MET–: 1.4 [1.4–2.7]	NA	CR: 0 PR: 8 (all MET+) SD: 43 PD: 48 NA: 10		MET+: 18% MET–: NA

CI = confidence interval; CR = complete response; HR = hazard ratio; IFN-a = interferon alpha; ITT = intention to treat subgroup; pRCC = papillary renal cell carcinoma; chRCC = chromophobe renal cell carcinoma; RMC = renal medullary carcinoma; ccRCC = clear-cell renal cell carcinoma; uRCC = unclassified renal cell carcinoma; TRCC = translocation renal cell carcinoma; NA = not applicable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RKC = rare kidney cancer; SD = stable disease.
[a] 80% CI.
[b] Subgroup of RKC.

survival (OS) was 12.8 versus 22.3 mo ($p < 0.0001$) [9]. A systematic review of RKC subpopulations from randomized controlled trials (RCTs) had significantly lower response rates and poorer median progression-free survival (PFS) and OS when compared with the predominant ccRCC population included in the same trials [10].

A phase II study of everolimus in pRCC patients (RAPTOR) reported clinical benefits; among patients with type 1 or type 2 histology, median PFS was 7.9 and 5.1 mo, respectively [11]. Two RCTs recruiting only RKC patients compared sunitinib with everolimus (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non–clear

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Cell Renal Cell Carcinoma [ESPN] and Everolimus Versus Sunitinib for Patients with Metastatic Non-clear Cell Renal Cell Carcinoma [ASPEN]) [12,13], and one RCT recruiting RKC and ccRCC patients comparing the same drugs but reporting the results for each subgroup separately (RECORD-3) provided some of the strongest data to date [14]. The median PFS in rare RCC patients for sunitinib and everolimus groups was 6.1 versus 4.1 mo for ESPN, 8.3 versus 5.6 mo for ASPEN, and 7.2 versus 5.1 mo for RECORD-3. The French phase II SUPAP (Sunitinib as First-line Therapy in Treating Patients with Locally Advanced Metastatic Papillary Renal Cell Cancer) trial also demonstrated sunitinib activity in pRCC patients with a median PFS of 6.6 mo in 15 type 1 and 5.5 mo in 46 type 2 pRCC patients [15]. The EAU RCC Guideline Panel recommends sunitinib over everolimus and temsirolimus for metastatic RKCs in first-line treatment, based on a systemic review [4]. As sunitinib is only modestly effective, and there is a lack of evidence for the use of other agents routinely used in ccRCCs such as pazopanib, axitinib, cabozantinib, and nivolumab, patients with RKCs should be referred as early as possible (eg, upon confirmation of pathology) to clinical trials when available.

3.3. *New insights from The Cancer Genomic Atlas and genomic analysis*

Research identifying druggable pathways involved in ccRCCs assists in the development of therapies based on genetic and molecular tumor characteristics [16] (Fig. 1). Genomic analysis of somatic mutations in RKCs revealed additional genes involved in pRCC and chRCC subtypes as possible therapeutic targets, including gene sets that could be used to stratify patients in clinical trials [17,18]. A pan-RCC comprehensive molecular analysis using five genomic platforms was performed on the three TCGA (The Cancer Genomic Atlas) datasets ($n = 894$ primary RCCs). Nine distinct subtypes were identified as common with many samples sharing greater molecular similarity with tumors that were grouped in different histological categories [19]. The authors found substantial molecular diversity even within each major subtype and an association with patient survival. In another series, exome, transcriptome, and copy number alteration data were collected from 167 primary renal tumors that included oncocytomas, pRCC, chRCC, and translocation subtypes. In pRCCs, variants in genes were significantly associated: *MET*, *NF2*, *SLC5A3*, *PNKD*, and *CPQ*. *MET* mutations occurred in 15% of the pRCCs analyzed and included previously unreported recurrent activating mutations. Variants in *TP53*, *PTEN*, *FAAH2*, *PDHB*, *PDXDC1*, and *ZNF765* were significantly associated with chRCCs. Gene expression analysis identified a five-gene set that allows classification of chromophobe, papillary, and oncocytoma subtypes. RNA sequencing also identified previously unreported gene fusions, such as *ACTG1-MITF* fusion, which leads to cellular transformation and expression of downstream target genes. Upregulation of *BIRC7*, an antiapoptotic factor, in MiTF-high RCC tumors suggests a potential therapeutic implications for BIRC7 inhibitors [18].

Papillary RCCs are the second most commonly encountered subtype in RCCs and has traditionally been subdivided into two types based on light microscopy [2]. The TCGA consortium molecularly characterized 161 pRCCs, using whole-exome sequencing, copy number analysis, messenger RNA/microRNA sequencing, DNA methylation analysis, and proteomic analyses. Type 1 tumors were associated with *MET* alterations, and gain of chromosomes 7 and 17, whereas type 2 tumors were characterized by *CDKN2A* silencing, *SETD2* mutations, *TFE3*/Xp11.2 fusions, and increased expression of the NRF2-antioxidant response element pathway. Interestingly, within type 2 pRCC, further subgroups could be distinguished on the basis of molecular

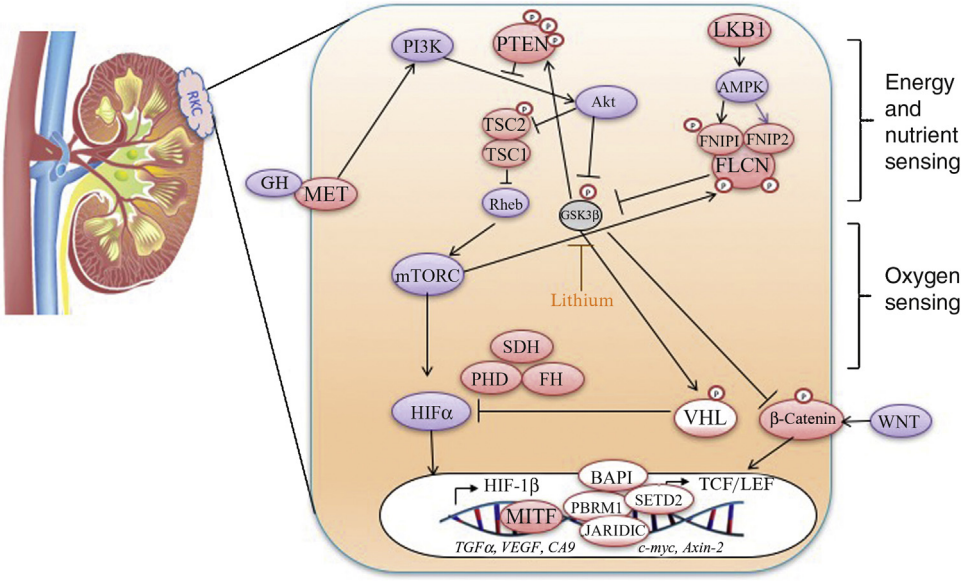

Fig. 1 – Pathways driving most subtypes of RCCs converge on nutrient- and/or oxygen-sensing pathways in the renal cell. Pink circles indicate proteins whose genes are mutated in rare kidney cancers (RKCs), and clear circles indicate genes mutated in clear-cell RCCs. RCC = renal cell carcinoma.

differences, which were associated with patient survival. A CpG island methylator phenotype was observed in a distinct subgroup of type 2 pRCCs, many with a germline mutation in the gene encoding fumarate hydratase (*FH*), characterized by early disease onset and poor survival [17].

Oncocytomas are predominantly benign neoplasms known for their accumulation of respiration-defective mitochondria. Using exome and transcriptome sequencing, Joshi et al [20] identified two main subtypes of renal oncocytoma, of which type 2 possibly progresses to more aggressive eosinophilic chRCC, although data are limited. Chromophobe RCCs can be difficult to distinguish from oncocytoma and cannot be graded by the Fuhrman grading system because of its innate nuclear atypia. Several alternative grading systems have been proposed, some of them validated [2,21,22]. Losses of chromosomes Y, 1, 2, 6, 10, 13, 17, and 21 are typical genetic changes [2]. Recently, TCGA investigated the landscape of somatic genomic alterations of 66 chRCCs based on mitochondrial DNA and whole-genome sequencing. Mitochondrial DNA sequencing revealed loss-of-function mutations in nicotinamide adenine dinucleotide dehydrogenase subunits, suggesting changes in mitochondrial function as a driver of the disease biology. In addition, recurrent structural breakpoints within the telomerase (*TERT*) promoter region correlated with highly elevated *TERT* expression [23,24].

Unclassified RCCs (uRCCs)—the subset of histologies defying standard classification—present formidable diagnostic and management challenges. Chen et al [25] reported a molecular analysis of 62 high-grade primary uRCCs, incorporating targeted cancer gene sequencing, RNA sequencing, single-nucleotide polymorphism array, fluorescence in situ hybridization, immunohistochemistry, and cell-based assays. They identified recurrent somatic mutations in 29 genes, including *NF2* (18%), *SETD2* (18%), *BAP1* (13%), *KMT2C* (10%), and *MTOR* (8%). Integrated platform analysis reveals that 26% uRCCs characterized by *NF2* loss and dysregulated Hippo-YAP signaling are associated with worse survival, whereas 21% uRCCs with mutations of *MTOR*, *TSC1*, *TSC2*, or *PTEN* and hyperactive mTORC1 signaling have a better clinical outcome. FH deficiency (6%), chromatin/DNA damage regulator mutations (21%), and ALK translocation (2%) distinguish additional cases. This study reveals distinct molecular subsets for 76% of the uRCC cohort, with potential diagnostic and therapeutic implications.

The value of data derived from the TCGA consortium lies in resource building for future explorations of other kidney tumors. Large consortia that catalog the metabolic, genomic, and structural alterations and cellular factors of RKCs may profit from these resources. The next step has already begun: using the catalog to generate novel hypotheses about how subtype-specific targeted therapy can be used to treat these patients.

3.4. *Potential "druggable" pathways*

The lower response rates to VEGF-targeted therapy likely reflect the lack of *VHL* loss in RKCs and a more heterogeneous etiology. The *MET* oncogene pathway in pRCC is an example of what could become a pathway-driven subtype-specific approach. Initially thought to be responsible in hereditary forms and to a lesser extent in sporadic pRCC type 1, *MET* has recently been reported to be altered across both sporadic pRCC types in a high percentage of 220 cases analyzed [26]. In a comprehensive analysis of rare kidney tumor samples with next-generation sequencing, pRCCs had frequent amplification, mutation, or overexpression of *MET* [18]. Remarkably, even among the phenotypically distinct type 2 pRCCs, *MET* alterations have been described [17]. Antibodies antagonizing the MET receptor–ligand coupling, such as AMG102, has been tested in a phase I trial of 40 patients with advanced solid MET-ligand hepatocyte growth factor (HGF)–dependent tumors in six sequential dose-escalation cohorts and one dose-expansion cohort [27,28]. The maximum tolerated dose was not reached, although dose-limiting hypoxia and dyspnea, and gastrointestinal hemorrhage were observed at lower dosages. Sixteen of 23 (70%) evaluable patients had stable disease (SD) for 7.9–40 wk but no Response Evaluation Criteria in Solid Tumors (RECIST) objective responses were observed. In a phase II study in patients with advanced RCCs including 11.5% papillary and 4.9% chromophobe subtypes (NCT00422019), AMG102 was tolerated, but it remained uncertain if the drug was growth inhibitory in this mixed-subtype population [29]. Monoclonal antibodies directed against the MET receptor itself, MetMAb/onartuzumab (PRO143966), have revealed promising results in preclinical and phase I studies [30]. A safety study of MetMAb (PRO143966) has been completed in patients with locally advanced or metastatic solid tumors (NCT01068977). However, none of these monoclonal antibodies is currently being tested in trials involving patients with type 1 pRCCs. Foretinib, an oral broad kinase inhibitor targeting MET among other receptors, was studied in a 74-patient phase II biomarker study, and it resulted in a median PFS of 9.3 mo [31]. The study showed that the objective response rate (ORR) for patients with germline or somatic *MET* mutation was 50% and 20%, respectively, versus only 8.8% in those without [31]. Disrupting the intracellular signaling pathways downstream of MET activity has been suggested as another treatment strategy [32]. Very recent data suggest that MET activity predicts response to savolitinib in a phase II single-arm study in 111 metastatic pRCC patient tumors. Tumor tissue sequencing determined that 44 patients had MET-driven pRCCs, which correlated with significantly better PFS and ORR with savolitinib in patients with MET-driven pRCCs compared with MET-independent disease (6.2 mo and 18% vs 1.4 mo and 0%, $p < 0.0001$) [33].

While the ESPN and ASPEN trials do not show significant activity with everolimus, it was suggested that proliferation could be inhibited by dual inhibition of phosphatidylinositol 3-kinase (PI3K) and mTOR based on preclinical models showing efficacy on cell proliferation, growth, cell survival, and angiogenesis [34]. A striking treatment benefit was recently observed in a phase II study of everolimus plus bevacizumab in patients with advanced RKCs. Interestingly, the presence of papillary features was associated with a benefit and correlated with ORR (43% vs 11%) and median

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PFS (12.9 vs 1.9 mo) [35]. Unfortunately, a phase Ib study of a dual PI3K–mTOR inhibitor in patients with advanced RCC of any subtype revealed significant toxicity without objective responses [36–38]. Collectively, data support the notion that pRCC should be stratified according to *MET* alteration status. A randomized phase II study projected to accrue 180 patients will perform comprehensive genomic profiling and measure efficacy of MET kinase inhibitors (cabozantinib, crizotinib, and savolitinib), each compared with sunitinib in metastatic pRCC (PAPMET; NCT02761057). Owing to its sample size, PAPMET will establish a prognostic and predictive value of designation of papillary subtype and markers of dysregulated MET signaling. Similarly, gene expression studies revealed MYC pathway activation in high-grade type 2 pRCCs, suggesting that the aggressive phenotype of type 2 pRCCs may be influenced by inhibition of components of the MYC signaling pathway [39].

In patients with HLRCC (with a distinct RCC entity resembling pRCC type 2; pathological hallmark is large nuclei with prominent orangeophilic nucleoli), a defect in the gene encoding the Krebs cycle enzyme fumarate hydratase *FH*, generates a pseudohypoxic state and upregulation of hypoxia-inducible factor target genes, similar to ccRCCs. Germline mutations in succinate dehydrogenase B are likewise associated with nonsyndromic RCCs [40]. Dual VEGF/epidermal growth factor receptor blockade with bevacizumab and erlotinib in patients with advanced HLRCC-associated RCC or sporadic pRCC is currently being tested in a phase II trial (NCT01130519; Table 2). Data from the first 41 patients enrolled were recently presented, including 20 with HLRCC-associated kidney cancer and 21 with sporadic forms of pRCCs. In the HLRCC cohort, an overall response rate of 65% was noted, while the response rate in the sporadic population was 29%.

Further evidence has been gathered for chRCC and translocation tumors. Pathway analysis highlighted clinically relevant dysregulated pathways of c-erbB2 and mTOR signaling in chRCCs [41]. The chRCCs are associated with germline *FLCN* loss in BHD syndrome and germline mutation of *PTEN* in Cowden syndrome [42]. An FLCN-interacting protein, FNIP1, interacts with 5′ AMP-activated protein kinase, a molecule for energy sensing that negatively regulates mTOR activity [43]. In vivo BHD murine models treated with rapamycin validate the potential of mTOR inhibitors for treating patients with BHD syndrome, although it is unclear whether this strategy is relevant for the more common sporadic chRCCs [44]. As mentioned above, molecular analysis of 66 sporadic chRCCs implicated changes in mitochondrial function and elevated *TERT* expression in chRCCs. Only two significant genes were found to be mutated in this cohort: *TP53* (32%) and *PTEN* (9%) [23]. In RCCs of all subtypes with sarcomatoid dedifferentiation, *TP53* (42.3%), *VHL* (34.6%), *CDKN2A* (26.9%), and *NF2* (19.2%) were the most frequently altered genes [45]. Since *TP53* is relatively rarely mutated in ccRCCs [46], the presence of such frequent mutations may suggest alternative treatment pathways similar to other *TP53*-mutated tumors.

FLCN inactivation and upregulation of *KIT* are also associated with chRCCs [47]. KIT-targeting drugs, including sorafenib, are not being currently tested in clinical trials specifically involving chRCCs. In a phase II trial involving 14 patients with advanced RCC treated with imatinib, only one patient had chRCC. This was the only KIT-positive tumor, and treatment with imatinib resulted in SD for 6 mo [48]. An exploratory analysis in the ESPN trial showed that median OS was longer with both sunitinib and everolimus for patients with chRCCs. In one patient with chRCC, a 58% decrease in tumor diameter with everolimus appeared to be associated with a *TSC2* mutation, which underscores the need for molecular characterization of each tumor [12]. In the ASPEN study, a median PFS of 11.4 mo was reported for chRCCs with everolimus versus 5.5 mo with sunitinib [13].

Translocation RCCs (TRCCs) are characterized by translocations resulting in gene fusions involving the *TFE3* transcription factor gene (Xp11.2) [49], *TFEB* (6p21), or *MITF* (3p13) with other genes. TRCCs display a distinctive gene expression signature as compared with other RCC types and harbor activation of *MITF*, transforming growth factor β1, and PI3K complex targets [49]. Tissue microarrays from 21 Xp11.2TRCCs, seven ccRCCs, and six pRCCs revealed elevated expression of phosphorylated S6 in TRCCs, suggesting that the mTOR pathway may be a potential therapeutic target [50]. Furthermore, induction of *MET* by translocation fusion gene products involved in TRCC results in strong MET autophosphorylation and activation of downstream signaling in the presence of HGF. In malignant cell lines containing endogenous TFE3 fusion proteins, inhibiting MET by RNA interference or by the inhibitor PHA665752 abolishes HGF-dependent MET activation, causing decreased cell growth. MET is thought to possibly be an additional potential therapeutic target for this tumor subtype [51]. Adult TRCCs appear to be different genetically from pediatric TRCCs and are characterized genomically by 17q gain in addition to MITF-family translocation [52]. Choueiri et al [53] analyzed 15 adults with advanced TRCCs of whom 10, three, and two received sunitinib, sorafenib, and monoclonal anti-VEGF antibodies, respectively. Three patients had a partial response (PR), seven SD, and five progressive disease. The median tumor reduction was 4.5% (range: 48% shrinkage to 67% growth). Median PFS and OS of the entire cohort were 7.13 and 14.3 mo, respectively. Malouf et al [54] reported on 21 patients with metastatic TRCCs who received systemic therapy. Seven patients achieved an objective response. In first line, median PFS was 8.2 mo for sunitinib ($n = 11$) versus 2 mo for cytokines ($n = 9$). In second line, three patients receiving sunitinib had a PR (median PFS 11 mo), seven of eight patients receiving sorafenib had SD (median PFS 6 mo), and of seven patients receiving mTOR inhibitors one had a PR and six SD. Median OS was 27 mo with a 19-mo median follow-up [54]. Currently, patients of all age groups with TRCCs are being enrolled in a randomized phase II trial of axitinib with pembrolizumab versus single-agent axitinib or pembrolizumab in a children's oncology group study for the treatment of TFE/TRCCs (AREN 1621) [55].

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Table 2 – Ongoing trials including exclusively or in part patients with RKCs for advanced or metastatic disease

Trial	Design and line	Included subtypes	Estimated enrollment (*n*)	Treatment	Primary end points	Secondary end points
PAPMET NCT02761057	Randomized Phase 2 One prior systemic therapy allowed except study drugs	pRCC types 1 and 2	180	Sunitinib versus cabozantinib versus crizotinib versus savolitinib	PFS	AE rate OS ORR MET mutation rate
SAVOIR NCT03091192	Randomized Phase 3 any line allowed except study drugs	pRCC any type, MET-driven only after screening	180	Sunitinib versus savolitinib	PFS	PRO AE rate OS ORR
CALYPSO NCT02819596	Randomized Phases 1 and 2 pRCC cohort: VEGF treatment-naïve or treatment refractory	pRCC and clear-cell RCC	195	Savolitinib versus durvalumab versus savolitinib + durvalumab versus tremelimumab + durvalumab	Phase 1 DLT ORR	Phase 1 PK Phase 2 PFS OS DOR Biomarkers
SUNNIFORECAST NCT03075423	Randomized Phase 2 Treatment naïve	Non-ccRCC with at least 50% non-cc component	306	Nivolumab + Ipilimumab versus sunitinib	OS rate at 12 mo	OS rate 6/18 mo OS PFS ORR AE rate QoL
NCT02724878	Single arm Phase 2 Prior VEGFR-TKI or cytokines allowed	pRCC any type chRCC Translocation CDC RMC uRCC Any histology with ≥20% sarcomatoid	40	Atezolizumab + bevacizumab	ORR	DOR AE rate IORR PFS OS QoL
NCT02915783	Single arm Phase 2 Treatment naïve	pRCC any type chRCC CDC RMC uRCC	31	Lenvatinib + everolimus	ORR	PFS OS
NCT01130519	Single arm Phase 2 No more than two prior systemic therapies excluding bevacizumab	Cohort A: HLRCC Cohort B: sporadic pRCC	85	Bevacizumab + erlotinib	ORR	PFS OS DOR Biomarkers Somatic FH mutations Effect on leimyomas
Keynote-427 NCT02853344	Single arm Phase 2 Treatment naïve	Cohort A: ccRCC Cohort B: non-ccRCC with or without sarcomatoid	255	Pembrolizumab	ORR	DOR PFS OS AE rate
Checkmate 920 NCT02982954	Nonrandomized Phase 3b/4 Treatment naïve	Cohorts: ccRCC KPS >70% Non-ccRCC KPS >70% Any RCC KPS 50–60% Any RCC with nonactive brain mets	200	Nivolumab + ipilimumab	High-grade IMAE	Time to IMAE PFS ORR TTR DOR
NCT01767636	Single arm Phase 2 One prior systemic therapy allowed	pRCC any type chRCC CDC RMC Translocation Sarcomatoid	39	Pazopanib	OS rate at 12 mo	AE rate PFS ORR
NCT01672775	Single arm Phase 1 Treatment naïve for non-ccRCC	ccRCC and non-ccRCC ENPP3-positive at prescreening Expansion cohort with ENPP3 + pRCC	34	AGS-16C3F at various dose levels	AE rate	PK ORR Antibodies against AGS-16C3F

FH = fumarate hydratase; HLRCC = hereditary leiomyomatosis and renal cell cancer; KPS = Karnofsky performance status; pRCC = papillary renal cell carcinoma; chRCC = chromophobe renal cell carcinoma; CDC = collecting duct carcinoma; RMC = renal medullary carcinoma; ccRCC = clear-cell renal cell carcinoma; uRCC = unclassified renal cell carcinoma; PFS = progression free survival; OS = overall survival; ORR = objective response rate; IORR = immune-related objective response rate; AE = adverse event; IMAE = immune-mediated adverse events; DLT = dose-limiting toxicity; PK = pharmacokinetics; DOR = duration of response; TTR = time to response; QoL = quality of life; ENPP3 = ectonucleotide pyrophosphatase/phosphodiesterase family member 3; PRO = patient-related outcomes; RKC = rare kidney cancer; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor.

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Very little progress has been made for the extremely rare carcinoma of the collecting ducts of Bellini and renal medullary carcinoma (RMC). For collecting duct tumors, the Groupe d'Etudes des Tumeurs Uro-Génitales performed a phase II study of gemcitabine plus platinum suggesting limited efficacy [56]. For RMC, a different chemotherapy regimen including cyclophosphamide, doxorubicin, cisplatin, topotecan, methotrexate, and vinblastine has been reported with very limited efficacy in retrospective series (Supplementary Table 2). Treatment of both tumor entities is an unmet need.

4. Conclusions

4.1. Organization of care

Multiple noncomparative studies suggest that RKC subtypes require an individual subtype and gene analysis–driven approach to improve therapeutic strategies in the future. Owing to small sample size, many of these studies are hypothesis generating at best, and multi-institutional cooperation is required to conduct studies for selected subtypes. Optimal care of patients with RKC would be in specialized centers experienced in clinical trials and personalized medicine, and for hereditary RCC syndromes, also capable of multidisciplinary care.

Prompt referral of patients with RKC, preferably immediately after pathological examination, to expert centers for surveillance and data collection is in the best interest of all stakeholders. Central pathology review is also recommended for RKC tumors. Registries such as the International mRCC Database Consortium or the USA-based National Clinical Trials Network biorepository can help identify patients with rare tumors among a large pool of thousands of patients worldwide and centralize tissue specimens for important research that is not otherwise feasible in a single-institution setting. In order to support this goal, we have created a portal targeting RKCs' key stakeholders at http://rarekidneycancer.org. For scientists, the website is a source of clinical and research data, whereas physicians and patients can find information about RKCs and access a clinical trial search tool that currently indexes 309 clinical trials for RKCs. Rarekidneycancer.org is working with patient organizations to address common issues such as sharing resources to bring together biological samples for sequencing and patient outcome data with appropriate standardized information release forms.

4.2. Design of future trials

Therapies with combinations of targeted agents and immune checkpoint inhibitors that have shown efficacy in ccRCCs are currently being investigated in studies that enroll in part or exclusively patients with RKCs. For example, a phase IIIb/IV safety trial of nivolumab plus ipilimumab (CheckMate 920; NCT02982954) is ongoing and a phase II trial to evaluate efficacy and safety of lenvatinib in combination with everolimus (NCT02915783) will start recruitment soon. While it is laudable that potentially more effective therapies are being investigated for patients with RKCs, candidates with RKCs are indiscriminately eligible as long as they have one of the subtypes summarized under "non-ccRCCs". Subtype-dependent differences in OS have long been recognized [57]. A previous large-scale retrospective dataset in "non-ccRCCs" confirms similar results [9] as did a recent comprehensive molecular analysis [19]. Accordingly, patients with RKCs should no longer be included collectively in "non-ccRCC" trials solely based on light microscopy–based diagnosis. In addition to histological characterization, full analysis of genomic alterations will be crucial in RKCs. Regarding subsets, it is becoming increasingly important to stratify patients by their genetic lesions as opposed to phenotypic subtype. It will be important that these patients are treated in the context of multicenter trials to ensure sufficient power for meaningful results and conclusions. In addition, these studies should include subsets of reasonable size from which to draw definitive conclusions to avoid interpretation of small subgroups that severely limited the ASPEN and ESPN studies. Owing to its sample size, PAPMET ($n = 180$) will allow to assess the prognostic and predictive value of MET pathway dysregulation and papillary subtype in metastatic pRCC patients. Likewise, the first phase III biomarker-based RCC trial randomizes pRCC patients with *MET* alterations to savolitinib versus sunitinib (SAVOIR; NCT03091192). Owing to the relative paucity of patients with RKCs, prioritization of such trials is essential and should be strictly peer reviewed involving key stakeholders and other bodies of interest, making them accessible and referable, with a strong pathological, genomic, and biological program (pathology review, tissue banking, and genomic characterization) and international alternatives for countries with no trials.

Rarer tumors that cannot reach a critical number of patients should be enrolled in rare tumor trials, and real-world databases should collect information on these to get insights into activity. Alternatively, pharmaceutical companies and academic centers could consider treating RKCs as orphan diseases, which fall under different categories with regard to approval requirements (for European Medicines Agency and Food and Drug Administration). Direct outreach to the patient community using tools (eg, http://rarekidneycancer.org/ or timeline tool at https://crohnology.com/) will help in patient recruitment, and alternative trial design approaches could be utilized to focus on patient series.

4.3. Trials

There is a dearth of knowledge about RKCs: pathophysiological mechanisms that drive tumor growth, natural history of each RKC tumor subtype, and most importantly, effective treatment management strategies. This has led to the prevailing medical opinion that RKCs are difficult to treat. Knowledge sharing and supporting well-designed clinical trials are the only way forward to improve RKC management, and collaboration between academia and pharmaceutical industry will be particularly critical to achieve these goals. Even though urologists and oncologists

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are encouraged to participate in clinical trials, one major bottleneck is the lack of trials willing to accept RKC patients. Even trials specifically aimed at RCCs will exclude the vast majority RKCs. It is of utmost importance to communicate the need for these studies to pharmaceutical companies and academic centers.

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Appendix A. Supplementary data

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