Management of Metastatic Renal Cell Carcinoma with Variant Histologies

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KEYWORDS

• Non–clear cell renal cell carcinoma • Immune checkpoint inhibitors • Tyrosine kinase inhibitors

KEY POINTS

- Variant histology renal cell carcinoma (vRCC) encompasses various entities with different molecular features.
- Systemic therapies in patients with metastatic vRCC are generally less active than in patients with conventional clear-cell renal cell carcinoma.
- Cytoreductive nephrectomy in the metastatic setting should be considered on a case-by-case basis for vRCC considering the lack of prospective data.
- Therapies targeting angiogenesis have shown substantial response rates, but comparative trials are lacking for these rare tumors.
- Immune checkpoint inhibitors are being evaluated as monotherapy or combination with early evidence of durable benefit. Ongoing trials are underway and may further improve outcomes of patients with vRCC.

INTRODUCTION

Renal cell carcinoma (RCC) affects more than 400,000 patients worldwide, and half of these patients will ultimately harbor metastatic disease.[1] Most RCC are of the clear cell (ccRCC) subtype, characterized by alterations of *VHL* and subsequent activation of the hypoxia-inducible factor pathway, as well as chromatin remodeling genes *BAP1*, *PBRM1*, and *SETD2*. Conversely, up to 25% of RCCs belong to the heterogeneous group of non–clear cell RCC, or variant histology renal cell carcinoma (vRCC), which encompasses diseases with different biology and distinct natural history. The most frequent subtypes of vRCC include papillary, chromophobe, collecting duct, renal medullary carcinomas, Xp11 translocation carcinomas, and succinate dehydrogenase deficient renal carcinomas, some of which may occur in the context of familial predisposition syndromes (**Table 1**).[2]

vRCCs are generally associated with aggressive metastatic behavior, decreased survival, and poor response to treatment with targeted molecular therapies compared with conventional clear cell tumors.[3] Advances in the molecular characterization of vRCC and the surge of immunotherapy-based regimens have paved the way for new therapeutic developments that may durably improve outcomes of patients with vRCC. Herein the authors discuss the biological landscape of vRCC and review current and future therapeutic options for patients with metastatic vRCC.

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Urol Clin N Am 47 (2020) 319–327
https://doi.org/10.1016/j.ucl.2020.04.003

Table 1
Main biological alterations in variant histology renal cell carcinoma

RCC Type	Chromosomal Alterations	Main Molecular Alterations	Main Familial Predispositions
Papillary type I	Gain of chromosome 7, 17, deletion of 1p36	*MET*	Hereditary pRCC (*MET*)
Papillary type II	Loss of chromosome 9p21, 3p	*CDKN2A*, *SETD2*, BAP1, PBRM1, activation of NRF2-ARE, TFE3 fusions	HLRCC (*FH*)
Chromophobe	Loss of chromosome 1, 2, 6, 10, 13, 17, and 21	*TP53*, *PTEN*, *mTOR*, *TERT*	Birt-Hogg-Dubé syndrome (*FLCN*)
Collecting duct	DNA losses at 8p, 16p, 1p and 9p; gains at 13q	Mitochondrial genome alterations	
Renal medullary carcinoma		*SMARCB1*	Sickle cell trait
Xp11 translocation carcinoma	*TFE3* or *TFEB* rearrangements	*BIRC7* expression	

MAIN BIOLOGICAL FEATURES OF VARIANT HISTOLOGY RENAL CELL CARCINOMA

Papillary renal cell carcinoma (pRCC) is the most frequent type of vRCC and comprises 15% to 20% of all RCCs. These tumors had been further divided histologically into pRCC types 1 and 2, but the latter group actually encompasses tumors with heterogeneous biology.[2] Clinical behavior of pRCC ranges from indolent localized tumors to aggressive metastatic subtypes more frequently encountered in type 2 histologies.[4] Recurrent alterations in type 1 pRCC include gain of chromosome 7 and mutations of *MET*(7q31), present in 81% of tumors.[5] Molecular characterization of type 2 pRCC identified a diverse set of alterations to include high activation of the NRF2 antioxidant response pathway, *CDKN2A* alterations (25%) conferring adverse outcomes, CpG island methylator phenotype associated with early and aggressive onset, silencing of *CDKN2A* and frequent *FH* mutations, as well as mutations in chromatin modifying genes *SETD2*, *BAP1*, and *PBRM1*.[4]

Chromophobe renal cell carcinoma (chRCC) is the second most frequent vRCC, accounting for ~5% of all RCCs, and is notably characterized by mitochondrial alterations, multiple losses of heterozygosity involving chromosomes 1, 2, 6, 10, 13, 17, and 21, as well as *TP53* (33% to 58%) and *PTEN* mutations (9% to 24%).[6,7]

Rare variants of vRCC encompass the most aggressive tumors, which often result from single somatic driver mutations and occur earlier in life. Those include translocation RCC, characterized by rearrangements of the MiTF family transcription factors *TFE3* and *TFEB*, accounting for aggressive diseases arising in young patients; collecting duct carcinoma, notable for metabolic alterations as well as *CDKN2A* and Hippo member *NF2* alterations; and renal medullary carcinoma, in which loss of the chromatin remodeling gene *SMARCB1* has been identified as the main driver alteration.[8]

On top of molecular alterations that could foster the development of targeted molecular therapies, new data have emerged about the immunology of vRCC. These tumors generally feature infiltration by mononuclear cells and frequent programmed death-ligand 1 (PD-L1) expression on both tumor cells and tumor infiltrating immune cells.[9,10] As such, many types of vRCC appear to be immunogenic tumors and potentially amenable to therapeutic strategies based on immune checkpoint inhibitors.

THE ROLE OF NEPHRECTOMY IN METASTATIC VARIANT HISTOLOGY RENAL CELL CARCINOMA

Cytoreductive nephrectomy (CN) has long been standard of care in the management of advanced RCC based on data from SWOG 8949 and EORTC 30947, which compared interferon-α with or without nephrectomy in metastatic ccRCC.[11,12] However, the benefit in overall survival (OS) demonstrated in these trials[12] was not confirmed in the era of targeted molecular therapy. The CARMENA trial evaluated sunitinib versus immediate CN followed by sunitinib in patients with

intermediate- or poor-risk ccRCC. This study enrolled 450 patients and showed a median OS of 18.4 months with sunitinib alone compared with 13.9 months in the CN arm, demonstrating noninferiority of sunitinib alone.[13]

However, in the setting of vRCC, where therapy is less effective, the role of CN continues to be controversial. Notably, a retrospective study from the International Metastatic RCC Database Consortium (IMDC) showed that CN was associated with improved survival in advanced RCC patients (20.6 vs 9.5 months), including 196 patients with vRCC (15.3 vs 8.0 months).[14] Additional data in 353 pRCC revealed a similar OS benefit (16.3 vs 8.6 months),[15] whereas a study based on the Surveillance, Epidemiology, and End Results database between 2001 and 2014 in 851 advanced vRCC showed a reduction in 2-year cancer-specific mortality from 77% to 52.6% with a CN.[16] Considering the lack of prospective data in vRCC, the role of CN remains unsettled and should be discussed on a case-by-case basis. Data from ccRCC trials suggest that upfront CN may especially benefit patients with low extrarenal tumor burden and good performance status, as well as those with significant symptoms from the primary tumor.[17]

SYSTEMIC THERAPY FOR VARIANT HISTOLOGY RENAL CELL CARCINOMA

Targeted Molecular Therapies

Development of systemic therapies in vRCC has largely followed the management of ccRCC. Notably, several trials evaluating VEGFR-TKIs demonstrated some activity in vRCC (**Table 2**), but their activity pales in comparison to that in ccRCC, because survival remains commonly less than 18 months.[18] Two randomized phase 2 trials, ASPEN and ESPN, were conducted in a selected vRCC population to evaluate the VGFR-TKI sunitinib versus the mTOR inhibitor everolimus in the metastatic setting.[19,20] The ASPEN trial demonstrated a significant increase in median progression-free survival (PFS) in patients treated with sunitinib compared with everolimus (8.3 vs 5.6 months), but the effect seemed to differ between prognostic risk groups and histology. Indeed, median PFS was numerically superior with everolimus compared with sunitinib in patients with poor-risk tumors, as well as in patients with chRCC. There was no difference in OS between arms. ESPN included patients with vRCC or ccRCC with greater than 20% sarcomatoid features and did not show any difference in median PFS between sunitinib (6.1 months) and everolimus (4.1 months). Median OS was 16.2 months and 14.9 months in the sunitinib and everolimus groups, respectively.[20] Two additional randomized trials evaluated mTOR inhibitors in an unselected RCC population, including vRCC. The RECORD-3 trial evaluated the sequence sunitinib-everolimus versus everolimus-sunitinib and included 14% of patients with vRCC, in whom OS was similar between both arms, at 16.8 versus 16.2 months, respectively.[21] Finally, GLOBAL-ARCC evaluated temsirolimus versus interferon-α or both and included 20% of patients with vRCC, showing a median OS of 11.6 months with temsirolimus compared with 4.3 months with interferon-α in this population.[22,23]

These data established sunitinib as the preferred option for patients with advanced vRCC in clinical practice, although efficacy remains limited as suggested by other single-arm phase 2 trials showing objective response rates (ORR) less than 15% regardless of histology.[24,25] Prospective studies have since been reported for pazopanib and axitinib, hinting at more promising efficacy data. In 29 patients with advanced vRCC treated with pazopanib, of whom 66% harbored a papillary histology, 28% of patients responded and median PFS was 16.5 months.[26] A phase 2 trial of axitinib in 40 patients with advanced vRCC who had progressed on temsirolimus demonstrated a ORR of 37.5% with a median PFS of 7.4 months.[27] In another phase 2 trial including 44 patients with pRCC only, axitinib provided an ORR of 28.6% and a median PFS of 6.6 months.[28]Although the data are retrospective, cabozantinib is active in vRCC and is intriguing particularly in papillary subtypes given its MET inhibition. In a multicenter retrospective review of 112 patients, cabozantinib exhibited a response rate of 27% across vRCC subtypes with a median time to treatment failure of 6.7 months and a 12-month OS of 51%.[29]

Combinations of targeted molecular therapies have also been evaluated, showing interesting results in subsets of patients. The combination of everolimus with bevacizumab showed interesting activity and was well tolerated in 35 patients with advanced vRCC, including mostly papillary and unclassified tumors.[30] The overall response rate (ORR) was 29%, with a median PFS of 11 months and a median OS of 18.5 months in these aggressive tumor subtypes. The combination of erlotinib and bevacizumab has also been evaluated in sporadic pRCC as well as pRCC associated with hereditary leiomyomatosis and renal cell cancer (HLRCC), based on the alleged activity of erlotinib on tumor cell metabolism.[31] In this trial, ORR was 44% for the whole cohort (N = 41).[32,33] Importantly, ORR was up to 60% in the cohort of

Table 2
Results of selected prospective clinical trials in variant histology renal cell carcinoma

Clinical Trial	Treatment	Line of Treatment	Number of Patients Enrolled	Histology	ORR, %	PFS, mo	OS, mo
SUPAP[24]	Sunitinib	First line	61	pRCC	13 (type I) and 11 (type II)	6.6 (type I) and 5.5 (type II)	17.8 (type I) and 12.4 (type II)
RAPTOR[49]	Everolimus	First line	88	Metastatic pRCC	1	7.9 (type I) and 5.1 (type II)	28 (type I) and 24.2 (type II)
ESPN[20]	Sunitinib vs everolimus	First line	68	vRCC and ccRCC with >20% sarcomatoid features	9 vs 3	6.1 vs 4.1	16.2 vs 14.9
ASPEN[19]	Sunitinib vs everolimus	First line	108	vRCC	18 vs 9	8.3 vs 5.6	31.5 vs 13.2
RECORD-3[21]	Sunitinib-everolimus vs everolimus-sunitinib	First line	66/238 (vRCC/total)	vRCC and ccRCC	—	7.2 vs 5.1	16.8 vs 16.2
GLOBAL ARCC[22]	Temsirolimus vs interferon-α	First line	124/626 (vRCC/total)	vRCC and ccRCC	5 vs 8	7 vs 1.8	11.6 vs 4.3
Choueiri et al,[34] 2017	Savolitinib	Any line	109	pRCC	7	6.2 (MET driven) and 1.4 (MET independent)	—
KEYNOTE 427 (cohort B)[43]	Pembrolizumab	First line	165	vRCC	25	4.1	Not reached
McGregor et al,[44] 2019	Atezolizumab and bevacizumab	Any line	60	vRCC and ccRCC with >20% sarcomatoid features	33	8.3	Not reached

Abbreviation: ORR, objective response rate.

patients with HLRCC (N = 20), with a median PFS up to 24.2 months, establishing a compelling therapeutic option in these patients.

Recent efforts have aimed at MET, a recurrent driver in pRCC.[5] A biomarker-based, single-arm, phase 2 trial of the MET inhibitor savolitinib was conducted in 109 patients with metastatic pRCC, of whom 40% had driver alterations of *MET*.[34] MET-driven pRCC achieved significantly increased ORR (18% vs 0%) and median PFS (6.2 vs 1.4 months) compared with MET-independent pRCC, confirming antitumor activity of savolitinib in MET-driven tumors. Foretinib, a multikinase inhibitor of MET, AXL, and VEGFR, demonstrated antitumor activity in advanced pRCC, with median PFS of 9.3 months and ORR of 13.5% in a phase 2 single-arm trial.[35] Crizotinib, which inhibits MET, ALK, and ROS-1, provided 2 partial responses and 1 stable disease in 4 patients with MET-driven pRCC.[36] Tivantinib, developed as a selective MET inhibitor, was studied either alone or in combination with erlotinib but failed to show antitumor activity in either arm, leading to early discontinuation.[37] Although early results from the savolitinib and crizotinib trials could have foreshadowed a promising future for MET inhibitors in pRCC, phase 3 trials with these agents have been stopped prematurely. Indeed, the phase 3 trial SAVOIR comparing sunitinib to savolitinib in pRCC was discontinued because of slow enrollment, whereas the PAPMET trial comparing sunitinib to savolitinib, crizotinib, or cabozantinib prematurely closed the crizotinib and savolitinib arms. As such, targeting driver alterations in vRCC remains a challenge for future therapeutic developments.

Immune Checkpoint Inhibitors

Considering the current limitations of targeted molecular therapies in vRCC, the need for novel therapeutic strategies is essential in poor-risk patients. The alleged immunogenicity of these tumors[9] suggests that immune checkpoint inhibitors could take a leading role in the future management of vRCC.

Although the anti–programmed cell death-1 (PD-1) antibody nivolumab has been Food and Drug Administration approved since 2015 in ccRCC after demonstrating survival advantage over sunitinib in the second-line setting,[38] data on PD-1/PD-L1 inhibition in vRCC have been scant (see **Table 2**). A retrospective analysis of 41 patients with vRCC from 6 US cancer centers treated with nivolumab revealed encouraging activity with partial responses in 20%, although more than 50% had progressive disease as best response.[39] Accumulating further evidence, another retrospective study including 40 patients with vRCC or ccRCC with greater than 20% rhabdoid features treated with nivolumab showed a response rate of 22%, including 9% complete responses, with a median PFS of 4.9 months and a median OS of 21.7 months.[40] These results were particularly encouraging because these patients were heavily pretreated with up to 8 lines of previous anticancer therapies. Additional datasets confirmed response rates of up to 20%, predominantly in pRCC and translocation RCC, as well as in patients who did not receive prior lines of therapy.[41] One retrospective study confirmed some evidence of activity for PD-1/PD-L1 inhibitors in translocation RCC, with a 17% objective response rate in 24 patients regardless of lines of therapy.[42]

The cohort B of the KEYNOTE-427 trial, a single-arm, open-label, phase 2 study of pembrolizumab monotherapy in treatment-naïve advanced vRCC, was the first study to prospectively assess the efficacy of PD-1 inhibition in vRCC.[43] A total of 165 patients with previously untreated vRCC were included and received pembrolizumab every 3 weeks for 2 years or until progression or withdrawal. Main subsets of vRCC were papillary (71%), chromophobe (13%), and unclassified (16%). At a median follow-up of 11.1 months, 56% of patients discontinued pembrolizumab because of either progression or withdrawal. The response rate was 24.8%, including 8 complete responses and 33 partial responses, with different outcomes according to histologic subtype: 34.6% of patients with unclassified RCC had objective response, compared with 25.4% for pRCC and 13% for chRCC. However, response rates were similar between patients with favorable IMDC risk (28.3%) and patients with intermediate or poor IMDC risk (23.3%). Expression of PD-L1 on tumor and immune cells as measured through Freeman antibody appeared to impact efficacy, because the response rate was 33.3% in patients with a combined positive score $\geq$1 compared with 10.3% in patients with a combined positive score less than 1.[43]

Combinations of immune checkpoint inhibitors with other approved therapies aim to improve these promising results. The anti–PD-L1 antibody atezolizumab has been evaluated in combination with the anti-VEGF antibody bevacizumab in a phase 2 trial including 60 patients with either vRCC or ccRCC with greater than 20% sarcomatoid features,[44] who may have received previous systemic therapy (35%). Response rate was 26% in those patients with vRCC (N = 42). Median PFS was 8.3 months in the entire cohort, with a median time to response of 2.7 months (range

Table 3
Selected ongoing clinical trials including variant histology renal cell carcinoma

Clinical Trial	Study Design	Treatment	Histology	Primary Endpoint	Secondary Endpoint
NCT02761057 (PAPMET)	Phase 2, randomized	Cabozantinib, crizotinib, savolitinib, sunitinib	Metastatic papillary renal carcinoma	PFS	ORR, OS
NCT03091192 (SAVOIR)	Phase 3, randomized	Savolitinib, sunitinib	MET-driven metastatic pRCC	PFS	OS, ORR
NCT01130519	Phase 2, single arm	Bevacizumab and erlotinib	HLRCC, sporadic papillary cancer	ORR	PFS, OS, DOR
NCT02495103	Phase 1/2, nonrandomized	Vandetanib and metformin	HLRCC, SDH-associated RCC, sporadic pRCC	Safety, ORR	—
NCT03541902 (CABOSUN 2)	Phase 2, randomized	Cabozantinib, sunitinib	vRCC	PFS	ORR, OS
NCT03354884 (BONSAI)	Phase 2, single arm	Cabozantinib	Collecting duct RCC	ORR	PFS, OS
NCT03635892	Phase 2, single arm	Nivolumab and cabozantinib	vRCC	ORR	—
NCT03177239 (UNISoN)	Phase 2 single arm, sequential	Nivolumab followed by nivolumab and ipilimumab	vRCC	ORR	DOR, PFS
NCT03203473 (OMNIVORE)	Phase 2, nonrandomized	Nivolumab, ipilimumab	ccRCC and vRCC	Persistent PR or CR after discontinuation PD or SD that converts to PR or CR at 1 y with addition of ipilimumab	PFS, OS

Abbreviation: DOR, duration of response ; ORR, objective reponse rate.

1.2–11.1) and a median duration of response of 8.9 months (range 1.4–29). Median OS was not reached after a median follow-up of 13 months. In an exploratory analysis of 36 patients with archival tissue available for testing, PD-L1 expression on tumor cells appeared to be associated with response: 60% in patients with PD-L1 expression $\geq$1%, compared with 19% in PD-L1–negative patients. In addition, there was a phase 2 trial combining the anti–PD-L1 antibody durvalumab with savolitinib in patients with pRCC stratified according to PD-L1 and MET status.[45] Although responses were shown in 27% of patients, neither PD-L1 expression (cutoff >25% on immune cells) nor MET status was predictive of response or survival. More combinations of immune checkpoint inhibitors with or without TKI are currently under investigation in vRCC and have the potential to enter clinical practice in the near future (**Table 3**).

PERSPECTIVES

An improved understanding of vRCC has been made possible thanks to molecular characterization and identification of various oncogenic processes associated with distinct entities. However, translating these understandings into new therapeutic options is a work in progress. CN can continue to be considered in the management of vRCC given the lower efficacy of current systemic therapies. Targeted therapies and immune checkpoint inhibitors, alone or in combination, appear to be steadily improving outcomes of patients despite a lack of randomized trials, which are technically more challenging in this context of rare tumors. Reports of complete responses to immune checkpoint inhibitors have been particularly encouraging[46] and support the use of immunotherapy alone or in combination with VEGF inhibitors in the upfront management of RCC. Further collaborative efforts are needed to consent patients to larger-scale trials and study biomarkers of response to therapy. Ongoing trials exploring immunotherapy combinations and targeted approaches will be critical to advance the care of vRCC (see **Table 3**).

Biomarker-based trials, such as those evaluating MET inhibitors, have been plagued by poor accrual and early termination, although results are awaited from PAPMET. Additional work is needed to investigate potential predictors of response to immune checkpoint inhibitors. Although PD-L1 expression in vRCC has been reported to be associated with response to both immune checkpoint inhibitor monotherapy and combination with VEGF inhibitors, heterogeneity in its assessments as well as clinical benefit in PD-L1–negative patients raise questions about its applicability in clinical practice.[43,44] Gene expression signatures developed in ccRCC[47,48] and levels of lymphocyte infiltration[10] could potentially be useful for defining the immunogenic context of vRCC subtypes and identify tumors that could best benefit from immunotherapy-based approaches.

Ultimately, the promise of individualized treatment of patients with vRCC is yet to be fulfilled. However, it has become a burgeoning research field with active trials of several new therapeutic options that could yet provide durable benefit to these underserved patients.

ACKNOWLEDGMENTS

The authors acknowledge Kevin Pels for his assistance in preparing the article.

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