Non–Clear Cell Renal Cell Carcinoma, Part 2: Therapy

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Abstract: Non–clear cell renal cell carcinomas (RCCs) represent a heterogeneous group of diseases with distinct molecular drivers, histologies, and clinical outcomes. Their low incidence and heterogeneity have resulted in a lack of studies that address the optimal strategies for each subtype. This article (the second in a 2-part series) reviews the current targeted therapies approved for RCC, such as the vascular endothelial growth factor receptor tyrosine kinase inhibitors and the mammalian target of rapamycin inhibitors. Ongoing studies will provide more information regarding the role of these agents in non–clear cell RCC. Ultimately, enhanced understanding of genetic triggers and the development of more tailored treatments remain imperative to improve outcomes in non–clear cell RCC.

Introduction

This article addresses the treatment of non–clear cell renal cell carcinoma (RCC). Non–clear cell RCC includes but is not limited to papillary RCC, chromophobe RCC, collecting duct carcinoma (CDC), renal medullary carcinoma, and renal carcinoma associated with an Xp11.2 translocation. In addition, RCC can be characterized by the presence or absence of a sarcomatoid component (these subtypes are discussed in part 1 of this 2-part series).

Although most clear cell RCCs are sporadic and not attributable to von Hippel-Lindau disease, somatic inactivation of the *VHL* gene is present in the majority of cases[1] and results in altered VHL protein function. The VHL protein negatively regulates hypoxia-inducible factor, which activates genes involved in cell proliferation, neovascularization, and extracellular matrix formation.[2] Consequently, RCC represents one of the best clinical models for therapies designed to address alterations in this hypoxia-inducible pathway. Since 2005, multiple agents that target components of this pathway have been approved for the treatment of clear cell RCC. These agents are broadly known as the targeted molecular therapies and have demonstrated a wider range of efficacy and enhanced tolerability compared with traditional cytokine-based immunotherapies, such as interferon-α and high-dose interleukin-2. Seven targeted agents are now available: sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer/Onyx),

pazopanib (Votrient, GlaxoSmithKline), axitinib (Inlyta, Pfizer), everolimus (Afinitor, Novartis), temsirolimus (Torisel, Wyeth), and bevacizumab (Avastin, Genentech).[3-9] However, data are limited regarding the activity of these drugs in non–clear cell RCC histologies, because most of the clinical trials included only clear cell disease. Previous studies evaluating cytokines and cytotoxic chemotherapy in non–clear cell RCC have shown minimal activity, perhaps with the exception of chemotherapy with CDC.[10]

Treatment of Metastatic Disease

Once metastatic, non–clear cell RCC histologies are generally characterized by resistance to traditional systemic therapies, and survival rates are low.[10-12] Small studies, meta-analyses, expanded-access trials (Table 1), and ongoing prospective trials (Table 2) have tried to address the utility of various agents in non–clear cell RCC.

VEGF Pathway Targeted Agents in Non–Clear Cell RCC

Although loss of function of the *VHL* gene is not detected in non–clear cell RCC, vascular endothelial growth factor (VEGF) receptors and their ligands can be overexpressed in some subtypes, such as papillary RCC and chromophobe RCC.[13,14] However, in the reported retrospective series and prospective trials, the response rates with the tyrosine kinase inhibitors generally have been disappointing compared with those observed in clear cell RCC (Table 2).[11,12,15-28] One retrospective review of 21 patients with non–clear cell RCC treated with sunitinib reported a modest overall response rate (ORR) of 14.3%, and overall clinical benefit (objective response or disease stabilization) in 52.4%.[12] Choueiri and colleagues retrospectively compared the effects of sorafenib and sunitinib in 53 patients with papillary (77%) and chromophobe (23%) histologies.[15] Three (25%) of 12 chromophobe RCC patients achieved a response with sorafenib (n=2) or sunitinib (n=1). Median progression-free survival (PFS) was 10.6 months. In the papillary RCC subgroup, sunitinib achieved a better ORR and longer median PFS at 4.8% and 11.9 months, respectively, compared with sorafenib, which induced no objective responses and produced a median PFS of 5.1 months. Although the number of patients was too small to draw definitive conclusions, the prolonged PFS from sunitinib in papillary RCC was comparable to the data from the large phase 3 trial in treatment-naive, metastatic clear cell RCC patients.[3] Ethnicity and a patient's underlying genetics may also play a role in response. In a small retrospective analysis of 31 Korean patients, most of whom had type 2 papillary RCC, 11 patients (35%) achieved a partial response and 17 (55%) experienced disease stabilization.[16] Median PFS was 6.4 months, and median overall survival (OS) was 25.6 months.

The sorafenib expanded access trial provided further insight into the efficacy of sorafenib in 202 patients with non–clear cell RCC histologies.[18] In the 107 patients with papillary RCC, partial response and stable disease were observed in 3% and 81%, respectively. In the 20 chromophobe RCC patients, partial response and stable disease were observed in 5% and 85%, respectively. Overall, median PFS was 24 weeks in the non–clear cell RCC subset. In the sunitinib expanded access trial, which enrolled 4371 patients with RCC, 588 patients (13%) had non–clear cell RCC histologies, of whom 11% achieved an objective response.[19] Median PFS was 7.8 months, and median OS was 13.4 months. Two other prospective studies encompassing various subtypes of non–clear cell RCC (mostly papillary) have observed response rates of approximately 5%, and stable disease in 53% to 68% of patients.[11,20] Overall, chromophobe RCC appears to have better outcomes, consistent with its known better prognosis irrespective of treatment.[29]

In a prospective phase 2 study, the French Genito-Urinary Group (GETUG) specifically assessed response to VEGF inhibition using sunitinib in 28 treatment-naive patients with papillary RCC.[21] Response rate was evaluable in 22 of the 28 patients. Only 1 patient experienced a partial response, but the majority achieved disease stabilization (72.7%; n=16/22).

Despite the poor prognosis of Xp11.2 translocation carcinoma in adults, response to VEGF-targeted agents has been observed, as described in retrospective series and case reports.[22,23] Objective responses and PFS seem to be similar to or perhaps slightly lower than those reported for clear cell RCC, at 20% and 7.1 months, respectively.[23]

With respect to CDC, a few small series and case reports support the use of VEGF inhibitors.[24,25] In 1 report, partial response or stable disease was observed in 23% of the patients, and median OS was 4 months.[24] Given the aggressive, highly proliferative nature of CDC, platinum- or taxane-based chemotherapy is generally tried first; however, VEGF-targeted agents can be considered for patients unfit for chemotherapy or as second-line options.

VEGF inhibitors can also be effective in RCC with a sarcomatoid component.[26-28] One study with 23 patients receiving sunitinib observed objective responses in 30% and stable disease in 22%.[26] Another retrospective study analyzed responses to sunitinib, sorafenib, or bevacizumab alone or in combination.[27] Overall, 19% of the 43 patients experienced a partial response and nearly half had disease stabilization (49%). Patients with a sarcomatoid component of less than 20% achieved better outcomes.

mTOR Inhibitors

Several downstream effectors of the mammalian target of rapamycin (mTOR) pathway are overexpressed and possibly activated in clear cell RCC as well as the other

Table 1. Summary of Clinical Experience With Systemic Therapy in Non–Clear Cell RCC

Type of RCC	Therapy	Study Description	Patients, n	ORR	PFS, mo	OS, mo
Non-ccRCC, any type	Temsirolimus vs IFN-α[5,31]	Phase 3	73	8.3% vs 5.4%	7 vs 1.8	11.6 vs 4.3
	Everolimus[33,34]	Expanded access program	75	1.3%	—	—
	Everolimus[32]	Phase 2	49	10.2%	5.2	—
	Sunitinib[19]	Expanded access program	588	11%	7.8	13.4
	Sunitinib[12]	Retrospective study	21	14.3%	4.1	14.6
	Sunitinib[20]	Phase 2	23	4.5%	5.5	—
	Sunitinib[16]	Phase 2	31	36%	6.4	25.6
	Sorafenib[18]	Expanded access program	476	3%-5%	6	—
	Capecitabine[52]	Phase 2	51	26%	10.1	18.3
Non-ccRCC or ≥20% sarcomatoid component	Everolimus vs sunitinib[37]	Phase 2	68	0% vs 12%	4.1 vs 6.1	14.9 vs 16.2
	Sunitinib[11]	Phase 2	57	5%	Overall: 2.7 pRCC: 1.6 ChRCC: 12.7	Overall: 16.8
	Temsirolimus or everolimus[39]	Retrospective study	85	7%	Overall: 2.9 Sarcomatoid: 3.5	Overall: 8.7 Sarcomatoid: 8.2
Papillary	Sunitinib[21]	Phase 2	28	3.5%	—	—
	Sunitinib[17]	Retrospective study	74	—	5	12
	Foretinib[44]	Phase 2	74	13.5%	9.3	—
Papillary and chromophobe	Sunitinib or sorafenib[15]	Retrospective	53	10%	8.6	19.6
Collecting duct	Gemcitabine + platinum agent[53]	Phase 2	23	26%	7.1	10.5
	Gemcitabine + platinum agent + bevacizumab[55]	Phase 2	5	—	15.1	27.8
Sarcomatoid features	Gemcitabine + doxorubicin[58]	Phase 2	18	39%	—	—
	Gemcitabine + doxorubicin[56]	Phase 2	39	16%	3.5	8.8
	Ifosfamide + doxorubicin[60]	Phase 2	23	0%	2.2	3.9
	Sunitinib + gemcitabine[61]	Phase 2	39	26%	10	5
	Sorafenib after gemcitabine + doxorubicin[28]	Phase 2	15	0% on chemo, 11% on sorafenib	—	—
	Sunitinib[26]	Retrospective study	23	30%	5.7	15.7
	Sunitinib, sorafenib, bevacizumab (alone or in combination)[27]	Retrospective study	43	19%	5.3	11.8

ChRCC, chromophobe RCC; IFN-α, interferon-α; mo, months; non-ccRCC, non–clear cell renal cell carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pRCC, papillary RCC; RCC, renal cell carcinoma.

Table 2. Summary of Ongoing Studies in Non–Clear Cell Renal Cell Carcinoma

Type	Drug	Phase	Characteristics	Status	ClinicalTrials.gov
All non-cc	Axitinib	2	Single arm; previously treated with temsirolimus	Recruiting	NCT01798446
	Everolimus and bevacizumab	2	Single arm	Recruiting	NCT01399918
	Temsirolimus vs sunitinib	2	Randomized	Completed, results not available	NCT00979966
	Sunitinib	2	Single arm	Active, not recruiting	NCT00465179
	Everolimus vs sunitinib (ASPEN)	2	Randomized	Active, not recruiting	NCT01108445
	Sunitinib	2	Single arm	Active, not recruiting	NCT01034878
All non-cc or ≥20% sarcomatoid features	Everolimus vs sunitinib	2	Randomized	Active, not recruiting	NCT01185366
All non-cc except for CDC and sarcomatoid	Pazopanib	2	Single arm	Recruiting	NCT01538238
Papillary	Everolimus (RAPTOR)	2	Single arm	Recruiting	NCT00688753
	Pazopanib (PINCR)	2	Single arm	Recruiting	NCT01767636
	INC280	2	Single arm	Recruiting	NCT02019693
	Crizotinib	2	Single arm	Recruiting	NCT01524926
	AZD6094	2	Single arm	Recruiting	NCT02127710
	Erlotinib and bevacizumab	2	Single arm	Recruiting	NCT01130519
Papillary or clear cell	AGS-16C3F	1	Single arm	Recruiting	NCT01672775
Non-cc or clear cell	Panobinostat + sorafenib	1	Single arm	Recruiting	NCT01005797
	Azacitidine + bevacizumab	1/2	Single arm	Active, not recruiting	NCT00934440
Sarcomatoid	Capecitabine, gemcitabine, and bevacizumab	2	Single arm	Active, not recruiting	NCT00496587
	Sunitinib and gemcitabine	2	Single arm	Recruiting	NCT01164228

ASPEN, Phase II Study of Afinitor vs Sutent in Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma; CDC, collecting duct carcinoma; non-cc, non–clear cell renal cell carcinoma; PINCR, A Phase II Efficacy Trial of Pazopanib in Non-Clear Cell Metastatic Renal Cell Cancer; RAPTOR, RAD001 as Monotherapy in the Treatment of Advanced Papillary Renal Cell Tumors Program in Europe.

histologic subtypes.[30] The use of mTOR inhibitors in non–clear cell RCC was supported by a phase 3 registration trial that compared the efficacy and safety of temsirolimus alone vs temsirolimus in combination with interferon-α (IFN-α) or IFN-α alone for the first-line treatment of poor-prognosis RCC.[5] In all histologies, response rates were similarly low in all 3 arms, and ranged from 7% to 11%. However, median OS was significantly longer in the temsirolimus monotherapy arm compared with the other 2 arms (10.9 months for temsirolimus, 7.3 months for IFN-α, and 8.4 months for the combination; *P*=.0069). This study was notable for being the first phase 3 trial of the targeted therapies in RCC that permitted patients with non–clear cell RCC to enroll. Exploratory analyses of non–clear cell RCC and indeterminate histologies (~20% of the patients) showed comparable median OS between clear cell RCC and non–clear cell RCC at 10.7 months and 11.6 months, respectively.[31]

Everolimus has been prospectively tested in a small phase 2 study of 43 Asian patients and a large, expanded-access program (REACT; RAD001 Expanded Access Clinical Trial in RCC).[32,33] In the REACT study, 5.5% (n=75/1367) of patients had non–clear cell RCC. Everolimus elicited similar results in non–clear cell RCC as

compared with clear cell RCC.[33,34] The median treatment duration was approximately 3 months, and objective responses were similarly dismal in both the non–clear cell and clear cell histologies (1.3% vs 1.7%, respectively). Disease stabilization appears to be the hallmark of clinical benefit with the mTOR inhibitors, and similar rates were observed in the non–clear cell and clear cell cohorts (49.3% vs 51.6%, respectively).

Further indication of the general efficacy of first line mTOR inhibitors in non–clear cell RCC comes from an established international metastatic RCC (mRCC) database, in which retrospective analysis characterized their use and efficacy.[35] Of the 127 patients identified, 51 patients (40.2%) had non–clear cell RCC histology and 24 (18.9%) had sarcomatoid features. The majority received temsirolimus (73%). The principal reasons for first-line therapy with an mTOR inhibitor over VEGF blockade were poor-risk status, non–clear cell RCC histologies, and clinical trials. In non–clear cell disease, median PFS was 4.8 months for temsirolimus and 3.3 months for everolimus. Median OS was 14.3 months for temsirolimus and 20.6 months for everolimus in non–clear cell RCC.

A large randomized phase 2 study, RECORD-3 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily), compared first-line everolimus followed by sunitinib at progression with the standard sequence of first-line sunitinib followed by everolimus.[36] Of the 471 patients with metastatic RCC, 66 patients (14%) had non–clear cell RCC histology. Everolimus did not achieve noninferiority compared with sunitinib as a first-line therapy. Median PFS was shorter for first-line everolimus (7.9 months) than for first-line sunitinib (10.7 months). The non–clear cell RCC subgroup had a similarly inferior PFS in the everolimus arm (5.1 vs 7.2 months). Overall, the trial results supported the standard sequence of sunitinib followed by everolimus at progression.[36]

The ESPN trial (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma) was the first direct comparison of VEGF blockade and mTOR inhibition in treatment-naive, non–clear cell RCC.[37] All subtypes of non–clear cell RCC and clear cell RCC patients with at least a 20% sarcomatoid component were permitted. The primary objective was to assess whether everolimus would elicit an increase in PFS to 20 weeks, vs a baseline estimate of 12 weeks with sunitinib. Patients could cross over to the other arm at progression. Everolimus and sunitinib both yielded modest efficacy. Patients in the first-line sunitinib arm had trends for longer median PFS (6.1 vs 4.1 months) and OS (16.2 vs 14.9 months), but these were not statistically significant. The ORR for first-line therapy was observed only in patients with chromophobe histology and was 2.8% for everolimus and 6% for sunitinib. Compared with all histologies, patients with chromophobe RCC achieved a longer median OS (31.6 months in the sunitinib arm and 25.1 months in the everolimus arm).[37] Ultimately, this trial was discontinued early for futility at the interim analysis of OS.

The ongoing phase 2 ASPEN (Phase II Study of Afinitor vs. Sutent in Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma) trial continues to assess the antitumor activity of sunitinib and everolimus in non–clear cell disease. In this study, special emphasis is placed on papillary and chromophobe subtypes. Clear cell RCC with sarcomatoid differentiation, medullary carcinoma, and CDC are excluded (NCT01108445).

Pal and colleagues observed overexpression of Aurora A kinase and increased activity of the mTOR pathway in sarcomatoid areas of RCC samples.[38] For this reason, mTOR and Aurora kinase inhibitors may be reasonable therapeutic options for metastatic RCC with a sarcomatoid component. In 1 retrospective study including patients with clear cell RCC with sarcomatoid features, of the 23 patients with a sarcomatoid component, median PFS was 3.5 months and median OS was 8.2 months.[39]

MET Inhibitors

MET inhibition is a rational strategy in RCC.[40] Activating mutations of the *MET* gene are associated with the majority of hereditary papillary type 1 RCC and a small percentage of sporadic papillary RCC.[41,42] However, MET activation can occur in all types of papillary RCC owing to increased gene copy number or upregulation of coactivators.[42] Increased c-MET expression has been observed in clear cell RCC and may be explained by the fact that, at least in vitro, inactivating VHL evokes constitutive phosphorylation of MET.[43] It has been speculated that phosphorylation of the MET protein modifies the intercellular adherence structure, which may induce tumor cell proliferation and resultant oncogenesis.[43]

Several c-MET targeted agents have been tested in RCC, including foretinib, rilotumumab, tivantinib, and cabozantinib (Cometriq, Exelixis). Foretinib is a tyrosine kinase inhibitor targeting MET, VEGF, and multiple other receptors. In a phase 2 study of 74 papillary RCC patients, Choueiri and colleagues observed evidence of clinical efficacy.[44] Although the ORR of 13.5% did not meet the 25% predefined response rate, the PFS of 9.3 months compared favorably with the VEGF receptor inhibitor experience in clear cell disease. Moreover, the activity in patients with a MET germline mutation was especially notable, with 50% of patients achieving a partial response in contrast to 9% whose tumors did not express the mutation.[44]

Rilotumumab (AMG 102) is a fully human monoclonal antibody that specifically targets hepatocyte growth factor/scattered factor (HGF/SF). A phase 2 study was performed in 3 patients with metastatic RCC, including

all histologies, most of whom had disease refractory to prior systemic therapy.[45] Of 7 patients with papillary RCC, four had stable disease. No objective responses were elicited, and median PFS was 3.4 months.

Tivantinib is a selective, noncompetitive inhibitor of c-MET.[46] One of the 4 phase 1 solid tumor trials included 5 patients with non–clear cell RCC.[47] Stabilization of disease was the best response in 3 patients with non–clear cell RCC. Tivantinib was also evaluated in a phase 2 trial, in which 6 patients with Xp11.2 translocation RCC were enrolled.[48] Interestingly, the MET receptor gene is upregulated by microphthalmia transcription factor (MITF), making MET inhibitors logical for the treatment for MITF-associated tumors.[49] However, stable disease was achieved in only 3 patients with a disappointing PFS of 2 months, implying negligible efficacy in this aggressive disease.[48]

Cabozantinib, a multityrosine kinase inhibitor against multiple receptors, including c-MET and the VEGF receptor, has shown promise in clear cell RCC, with an ORR of 28% and median PFS of 12.9 months in a treatment-refractory population.[50] Ongoing phase 2 and 3 studies are evaluating this agent further in RCC (NCT01865747; NCT01835158).

Cytotoxic Chemotherapy

In general, RCC is thought to be resistant to cytotoxic chemotherapy, with objective responses generally elicited in less than 5% of patients.[51] Modest efficacy has been observed in small series and in more aggressive subtypes (Table 2). For example, in a phase 2 study of 51 patients with metastatic non–clear cell RCC, capecitabine showed activity with an objective response rate of 26% and disease stabilization in 47% of patients.[52] Median PFS was 10.1 months, and OS was 18.3 months. Responses to combination chemotherapy also have been reported in patients with CDC and sarcomatoid variants of RCC. A phase 2 trial reported that the combination of gemcitabine and platinum agents (cisplatin or carboplatin) was active in CDC.[53] In 23 patients, objective responses were achieved in 26%, including 1 complete response, and stable disease was achieved in 44%, for an overall clinical benefit rate of 70%. Median PFS was 7.1 months, and median OS was 10.5 months. One small series and 1 case report have demonstrated that the addition of bevacizumab in this combination was also effective and may enhance activity.[54,55] Of the 6 patients who were treated with cisplatin/gemcitabine/bevacizumab, there were 2 complete responses, 3 partial responses, and 1 case of stable disease. Median PFS was promising at 15.1 months, with a median OS of 27.8 months.[55]

Given the more aggressive nature of tumors with sarcomatoid differentiation, chemotherapeutic approaches with agents such as gemcitabine and doxorubicin have been attempted. Various studies have demonstrated objective response rates ranging from 16% to 39%, including some complete responses.[56-58] Conversely, a smaller study testing gemcitabine with doxorubicin[59] and another study with doxorubicin and ifosfamide did not produce any objective responses in these variants.[60] Chemotherapy often is used initially for patients with RCC with sarcomatoid differentiation. However, given the similar responses observed with the VEGF inhibitors at least retrospectively, first-line VEGF inhibition is also reasonable. Ongoing and maturing clinical trials are testing combinations of chemotherapy and VEGF blockade in RCC with sarcomatoid differentiation. The final results of a phase 2 trial testing sunitinib plus gemcitabine in sarcomatoid RCC or high-risk RCC were recently presented. In the group with the sarcomatoid component, the ORR was 26% and the SD was 38%.[61] An ongoing phase 2 cooperative group trial is evaluating sunitinib vs sunitinib/gemcitabine (NCT00556049). Finally, another phase 2 study is assessing the safety and efficacy of capecitabine and gemcitabine plus the VEGF antibody bevacizumab in patients with RCC with sarcomatoid differentiation (NCT00496587).

Cytoreductive Nephrectomy and Metastasectomy for Non–Clear Cell RCC

In the immunotherapy era, 2 randomized clinical trials demonstrated an OS benefit to adding cytoreductive nephrectomy prior to systemic therapy with IFN-α in patients with metastatic RCC.[62,63] Recently, 2 retrospective studies compared survival in patients with metastatic disease who had cytoreductive nephrectomy in addition to treatment with a targeted therapy.[64,65] Most patients appeared to benefit from primary tumor removal, except for those with poor prognostic features according to International mRCC Database Consortium (IMDC) criteria.[66] Two ongoing phase 3 trials are prospectively evaluating the importance of nephrectomy in metastatic clear cell RCC treated with sunitinib (NCT00930033; NCT01099423).

There are few data on the role of cytoreductive nephrectomy in metastatic non–clear cell RCC. In a retrospective population-based study of 591 non–clear cell RCC patients treated between 2000 and 2009, patients who underwent cytoreductive nephrectomy had lower cancer-specific and all-cause mortality than those who did not.[67] An interaction model found lower all-cause mortality for all histologies after cytoreductive nephrectomy. Another retrospective study has investigated the outcomes of cytoreductive nephrectomy for clear cell and non–clear cell RCC patients who had impaired performance status.[68] Only 37.5% of patients who had a low Eastern Cooperative Oncology Group (ECOG) performance score of 2 or 3 experienced an improvement in their performance status in the postoperative period and only 57.5% received postoperative systemic therapy. Median disease-specific survival for this subgroup was 6.6 months. The investigators did observe that a subset of patients with

an ECOG performance status of 2 or 3 who were symptomatic from bone metastasis may have derived greater benefit from cytoreductive nephrectomy than patients who were symptomatic owing to visceral metastases (median disease-specific survival: 17.7 months and 2.1 months, respectively; P=.006).[68] Collectively, these studies show that cytoreductive nephrectomy can be considered for non–clear cell RCC patients, especially when taking into account life expectancy, sites of metastases, and performance status.

In terms of metastasectomy for non–clear cell disease, there have been a few case reports that have demonstrated long-term survival after resection.[69,70] Larger series of all subtypes of RCC have shown that metastasectomy may improve OS and potentially elicit cure, especially in the setting of solitary or oligometastasis.[71,72] Several series of patients who underwent pulmonary metastasectomy have reported 5-year OS rates ranging from 38.5% to 83.3%.[73-75]

Thus, in the absence of standard systemic therapies, this approach may be appropriate for selected patients with minimal disease burden and slow progression, especially in subtypes that tend to be more clinically indolent, such as chromophobe RCC.

Summary and Future Directions

The available prospective and retrospective data suggest that the targeted agents currently approved for clear cell RCC can have activity in non–clear cell RCC. The phase 3 study of temsirolimus demonstrated a similar degree of benefit, as did the expanded access trials evaluating sunitinib, sorafenib, and everolimus in more real-world, generalizable patient populations.[5,18,19,31,33,34] In addition, despite their poor prognosis, CDC and RCC with sarcomatoid components appear to demonstrate some sensitivity to chemotherapy. Ongoing clinical trials may provide additional evidence for the role of combinations of the targeted therapies with cytotoxic chemotherapy in this subgroup of patients.

However, although these agents can be effective, they are in no way a "home run," and we remain with a paucity of effective systemic options for metastatic non–clear cell RCC. Thus, clinical investigation of novel therapeutics remains imperative. One such area of intense investigation in multiple solid tumors is inhibition of immune checkpoints, which may be reasonable targets in non–clear cell RCC. T cells express receptors critical to the control of the immune response. Programmed death 1 (PD-1) is an inhibitory receptor expressed on immune cells, including effector T cells.[76,77] One of its ligands, programmed death ligand 1 (PD-L1), can be expressed by multiple normal tissues and also by tumors, and may represent a mechanism by which these tumors elude the host immune system. When PD-L1 on the tumor binds to PD-1 on the effector T cell, it inactivates the T cell. Overexpression of PD-L1 has been linked to poor prognosis in various tumor types, including RCC.[78] Antibodies targeting PD-1 or PD-L1 have achieved clinical benefit in several small studies evaluating RCC, albeit mostly in clear cell disease.[79-81] Recently, Choueiri and colleagues observed variable PD-L1 expression rates in non–clear cell RCC with higher levels in CDC and translocation carcinomas at 20% and 30%, respectively, compared with 10% and 5.6% in papillary and chromophobe RCC.[82] Higher PD-L1 expression correlated with worse outcomes in non–clear cell RCC and was more common on the immune cells than on the tumor cell membrane.[82] Preliminary results from the ongoing phase 1 Genentech trial (NCT01375842) evaluating the PD-L1 antibody MPDL3280A observed an ORR of 17% and a 24-week PFS of 20% in 6 non–clear cell RCC patients.[83] This activity suggests that targeting the PD-1 pathway in non–clear cell RCC could be effective.

Diverse epigenetic alterations, such as histone modification and DNA methylation, can be involved in cancer development and progression.[84] In RCC, lower levels of histone methylation have been correlated with higher tumor grade and pathologic stage.[85] Targeting enzymes important in these epigenetic mechanisms may reverse the alterations and control tumor growth. In vitro, histone deacetylase (HDAC) inhibitors such as vorinostat (Zolinza, Merck), suberoylanilide hydroxamic acid (SAHA), and valproic acid have demonstrated cytotoxicity in RCC cell lines and synergy with other agents like everolimus.[86-88] In phase 1 and 2 studies, HDAC inhibitors alone or in combination with other drugs that are active in RCC, such as sorafenib, generally have been well tolerated in patients with RCC.[89-91] Response rates in heavily pretreated patients have been modest; however, prolonged disease stabilization can be observed. Another epigenetic mechanism that may play a role in RCC is the silencing of tumor suppressor genes by hypermethylation of the promoter region.[92] To reverse this silencing, demethylating agents such as azacitidine have been studied. In a phase 1 study of azacitidine plus the HDAC inhibitor valproic acid, 1 patient with rapidly progressive RCC experienced stable disease for 6 months.[93] The combination of azacitidine and bevacizumab also is under investigation in RCC (NCT00934440).

In summary, although the non–clear cell histologies are often lumped together as a single entity, they are distinct subtypes that likely have very different pathogenic drivers requiring more individualized treatments. Their less frequent occurrence has made large-scale investigation difficult. We are at the forefront of identifying molecular drivers of non–clear cell RCC, and thorough understanding of these alterations is critical to the development of appropriate treatment strategies. As such, clinical trials should be offered up front to all patients with non–clear cell RCC. In the absence of currently available evidence-based treatments, genetic tumor profiling may also help guide patients to rational therapies.

Disclosures

Drs Valenca and Hirsch have declared no financial conflicts of interest. Dr Choueiri has served on the advisory boards of Novartis, Pfizer, GlaxoSmithKline, Merck, Bristol-Myers Squibb, and Bayer. Dr Harshman has served on the advisory boards of Genentech, Bristol-Myers Squibb, Aveo, and Pfizer, and receives research funding or support from Pfizer and Medivation.

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