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Targeted Therapeutic Strategies for the Management of Renal Cell Carcinoma

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Summary

Agents targeting the VEGF and mTOR pathways remain the mainstay in the management of metastatic RCC. Understanding the importance of the VHL/HIF pathway in clear cell RCC has hitherto guided targeted therapy options in this disease, but other potential targets are beginning to emerge. Ongoing and future studies are expected to facilitate the development of therapeutic regimens which incorporate agents with improved tolerability and enhanced efficacy by continuing to capitalize on the strides made by basic and translational scientists in uncovering the mechanisms underlying the various forms of RCC.

Keywords

Renal cell carcinoma (RCC); clear cell; von Hippel-Lindau (VHL); Tuberous sclerosis (TS); Succinate dehydrogenase (SDH); Papillary; Hereditary papillary renal cancer (HPRC); Hereditary leiomyomatosis and renal cell carcinoma (HLRCC); Translocation carcinoma; Chromophobe; targeted therapy; tyrosine kinase inhibitor (TKI); vascular endothelial growth factor (VEGF); mammalian target of rapamycin (mTOR)

Introduction

Renal cell carcinoma (RCC) has a global impact. Approximately 111,100 new cases and 43,000 deaths from the disease were seen among men in developed countries in 2008 alone [1]. In the United States in 2011, RCC ranked as the sixth and eighth most common malignancy in men and women, respectively, with an estimated 60,920 new cases and 13,120 deaths [2]. Approximately 1 in 67 Americans face a diagnosis of renal malignancy during their lifetime [3].

Despite the proliferation of systemic targeted therapies designed to treat advanced RCC, durable complete responses (CRs) remain elusive [4–5]. This review will focus on recent clinical and pre-clinical reports that are likely to advance our ability to manage both clear and non-clear cell variants of RCC. (Table 1) Whenever possible, trials are identified by

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Purpose of review

This article reviews recent developments in the use of systemic targeted therapies for the treatment of advanced clear and non-clear cell renal cell carcinoma (RCC). The genetic/molecular basis of each form of RCC is discussed and current treatments and clinical trials are described.

their NCT number so the reader may easily find the study of interest on the National Institutes of Health's clinical trial registry website [6].

Clear Cell RCC

Clear cell RCC (ccRCC) is the most common histologic variant of RCC, comprising nearly 75% of all kidney cancers [7]. Based on the study of inherited clear cell kidney cancer, the kidney cancer gene *VHL* was identified in 1993 [8]. Subsequent work demonstrated loss of *VHL* in nearly 90% of sporadic ccRCC by either loss of heterozygosity (LOH), or epigenetic silencing [9]. More recently, mutations in a number of genes affecting chromatin remodeling have been identified in ccRCC. The most prevalent of these is the PBRM1 gene, which is mutated in approximately 40% of ccRCC tumors [10]. Further insights into these alterations and their role in ccRCC will likely improve our understanding of renal tumorigenesis and progression and lead to the development of novel therapeutic strategies.

Elucidation of the molecular pathways that are dysregulated following *VHL* tumor suppressor inactivation has opened the doors to an era of targeted therapy in the treatment of kidney cancer. Currently, 6 agents targeting this pathway, particularly components of VEGF signaling (sunitinib, sorafenib, pazopanib, bevacizumab + interferon- α) and the mTORC1 complex (temsirolimus, everolimus), are FDA approved for the treatment of advanced kidney cancer [11–17]. (Table 2) Most patients today receive a VEGF pathway antagonist, either sunitinib or pazopanib, as first line therapy for metastatic disease, based on the demonstration that these agents prolong PFS compared to interferon- α or placebo, respectively. Despite the availability of a number of agents with activity, the most effective second line therapy, as well the optimal sequencing of these agents, remain unclear.

Both sorafenib and pazopanib are associated with an improved PFS compared to placebo in patients who have previously received cytokine therapy. In patients who have progressed on first line therapy with a VEGF-pathway antagonist, everolimus was hitherto the only agent shown to offer clinical benefit (modest prolongation of PFS compared to placebo in a randomized phase III study) [16, 18]. (Table 2) Axitinib, a potent, selective, second generation VEGFR1,2,3 inhibitor, was the subject of the recently concluded phase III AXIS trial which compared its efficacy to sorafenib, a first generation VEGFR and RAF inhibitor, in the second line setting. Rini and colleagues reported on 723 patients with ccRCC treated at 175 sites in 22 countries who progressed on one first-line therapy containing sunitinib, bevacizumab, temsirolimus or cytokines and were then randomized to receive axitinib (N=361) or sorafenib (N=362) [19]. Median progression free survival (PFS), as measured by response criteria in solid tumors (RECIST), was 6.7 months in the axitinib arm compared to 4.7 months in the sorafenib arm (hazard ratio 0.665; 95% CI 0.544–0.812; $P<0.0001$). Treatment was discontinued because of adverse events (AE) in 4% of patients receiving axitinib versus 8% of patients treated with sorafenib.

The AXIS study also evaluated symptom deterioration by incorporating two validated survey instruments, the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) questionnaire and the FKSI–Disease-Related Symptoms (FKSI-DRS) subscale, which is specifically designed to measure symptoms associated with advanced RCC. Time to symptom deterioration was defined *a priori* as two consecutive decreases of 5 points from baseline using the FKSI or 3 points using FKSI-DRS, which are the established standards with these instruments [20–21]. Axitinib lengthened median time to symptom deterioration compared to sorafenib as measured by both the FKSI and FKSI-DRS (3.1 months vs. 2.8 months, $P<0.014$; and 3.7 months vs. 2.9 months, $P<0.02$, respectively). These data establish axitinib as a potential alternative in the second-line setting in ccRCC.

At the time of this review, axitinib had not received FDA approval, but was endorsed by the US FDA Oncology Drugs Advisory Committee in December 2011.

Other studies examining drugs in the second-line or subsequent setting include a phase III comparison of dovitinib, a multikinase inhibitor that has activity against the fibroblast growth factor receptor in addition to VEGFR, vs. sorafenib (NCT01223027) for patients with ccRCC who have failed both a VEGFR and mTOR agent. The primary endpoint is PFS by RECIST with a secondary endpoint of OS. The RECORD-3 trial is looking at the importance of sequencing active agents via a randomized, open-label, multicenter phase II study that compares everolimus-sunitinib vs. sunitinib-everolimus in treatment-naïve patients with metastatic RCC (NCT00903175). The primary endpoint is PFS after primary treatment. This trial is ongoing but not currently recruiting patients.

Papillary RCC

Papillary renal cell carcinoma (pRCC) is the second most common histologic subtype of RCC, accounting for approximately 15% of all RCC diagnoses [7]. Currently, two types of pRCC, type 1 and type 2, are recognized and differ in their histologic morphology and gene alterations. Both hereditary and sporadic forms of these subtypes have been described.

Type 1 papillary RCC

Hereditary papillary renal cancer (HPRC), the familial form of type 1 pRCC, is characterized by activating germline mutations of the *MET* oncogene located on chromosome 7q31. Somatic *MET* mutations have also been detected in 5–13% of sporadic pRCC [22]. The *MET* oncogene encodes a membrane spanning protein which serves as the receptor tyrosine kinase (RTK) for hepatocyte growth factor (HGF). *MET* undergoes autophosphorylation when stimulated by its ligand, HGF, leading to downstream activation of an intracellular cascade including PI3K and mTOR activation. *MET* has been implicated in motility, proliferation, angiogenesis and cell survival [23].

Several strategies targeting the *MET* pathway are being explored, including antibodies against HGF and *MET*, as well as inhibitors of *MET* kinase activity. AMG 102, a human antibody to an epitope in the beta-chain of HGF was evaluated in a phase II study of patients with advanced RCC [24]. Results from this trial were disappointing; only a single partial response was seen in the 61 patients treated at two dose-levels, and the PFS in both dosing cohorts was modest. However, it must be noted that this study included patients with all histologic subtypes of RCC and did not select patients based on evidence of *MET* pathway activation. Although AMG102 is unlikely to offer clinical benefit as a single agent in unselected patients, there may be a role for further evaluation of *MET* pathway antagonists in tumors with known *MET* pathway activation (NCT00422019).

Foretinib is a dual *MET* and VEGFR2 kinase inhibitor that is being currently evaluated in a phase II study of patients with RCC (NCT00726323). Unlike previous trials of *MET* pathway antagonists, this trial is restricted to patients with papillary histology (both type 1 and 2 histologies are included). In addition, patients enrolled on this trial will be stratified based on the presence of *MET* pathway activation to determine if *MET* status impacts on response to the agent. Based on an interim analysis, foretinib appears to be well tolerated and has activity in papillary RCC, with the majority of patients experiencing some degree of tumor regression [25–26]. The trial has completed accrual and final efficacy data as well as results from relevant biomarker analyses are expected soon.

Subgroup analyses of the papillary RCC patients enrolled in the global Advanced Renal Cell Carcinoma (ARCC) trial has led to an interest in evaluating mTOR inhibitors in this disease.

In this randomized phase III study, 55 patients with papillary RCC were identified. Those who received the mTOR inhibitor temsirolimus (N=25) had a better OS compared to patients who received interferon- α (N=30) [27–28]. Median OS was 10.9 months vs. 5.7 months and median PFS was 5.9 months vs. 2.1 months in the temsirolimus and interferon groups, respectively [28]. This data has led to the RAPTOR trial (RAD001 in Advanced Papillary Tumor Program in Europe, NCT00688753) which is evaluating the efficacy of everolimus, an oral mTOR inhibitor, in pRCC. RAPTOR is a single arm, non-randomized, multicenter phase II trial whose primary end point is PFS rate at 6 months. In the US, patients with advanced non-clear RCC histologies, including pRCC, can be enrolled in phase II trials comparing everolimus to sunitinib (NCT01185366 or NCT01108445).

Type 2 Papillary RCC

Type 2 pRCC includes a variety of morphologically similar tumors and is usually associated with a poor prognosis [29]. In a hereditary form of pRCC, patients have germline mutations of the gene encoding the Krebs cycle enzyme, fumarate hydratase (*FH*), which is located on chromosome 1. Patients with this condition, hereditary leiomyomatosis and renal cell carcinoma (HLRCC), have a propensity for developing cutaneous and uterine leiomyomas as well as a form of type 2 pRCC that is clinically aggressive with an early metastatic potential.

One well understood mechanism for the development of renal tumors in HLRCC patients is the acquisition of a “pseudo-hypoxic” drive resulting from VHL-independent HIF accumulation. Isaacs and colleagues demonstrated that loss of *FH* leads to accumulation of fumarate, a competitive inhibitor of prolyl hydroxylase, which is a critical enzyme required for hydroxylation of HIF and its subsequent binding to VHL [30]. Inhibition of prolyl hydroxylase interferes with VHL-dependent degradation of HIF and upregulation of hypoxia inducible genes [31]. Recently, in an HLRCC model, *FH* loss was shown to result in a loss of oxidative phosphorylation and a shift to aerobic glycolysis, the so called Warburg effect, as well as downregulation of cellular AMPK. The absence of *FH* and the resulting impairment of the Krebs cycle render *FH* $-/-$ cells extremely reliant on glycolysis and high ambient glucose for their energy needs [32].

It may be possible to exploit the reliance of *FH* $-/-$ tumors on glycolysis by targeting critical steps in the glycolytic process or by interfering with the delivery of glucose to tumor cells. Several inhibitors of key glycolytic steps as well as other components of tumor metabolism are currently being evaluated in preclinical models or early clinical trials. It may also be possible to alter glucose delivery to tumor cells by means such targeting tumor vasculature. This is the basis for a phase II trial of combined VEGF/EGFR inhibition with bevacizumab and erlotinib in patients with HLRCC-associated pRCC and sporadic pRCC currently open for accrual at the National Cancer Institute (NCT01130519) [33]. In addition to response and survival endpoints, the prevalence of somatic *FH* alterations will be analyzed in sporadic pRCC, to better understand the role of Krebs cycle defects in sporadic forms of pRCC.

Translocation RCC

Xp11 translocation RCC is one of the newly identified RCC variants added to the WHO 2004 classification [34]. Translocation carcinoma is the result of gene fusions of the TFE3 transcription factor gene with one of a variety of other genes [35–36]. Translocation tumors are typically considered a pediatric manifestation of RCC as they account for only a small percentage of adult kidney cancers [37]. These tumors overlap morphologically with clear cell and papillary RCC and the incidence of translocation carcinoma may be underestimated

in the absence of cytogenetic testing. These tumors are seen more commonly in younger, female patients, and tend to be clinically aggressive [38].

The TFE3 protein is involved in cell growth and proliferation. Recent data suggest that TFE3 may play a role in the TGF- β signaling pathway, and appears to be important in transcriptional activation of the plasminogen activator inhibitor-1 (PAI-1) via this pathway [39]. In addition, elevated expression of phosphorylated S6 has been described in translocation carcinomas, suggesting that the mTOR pathway may be a potential therapeutic target [40]. Lastly, TFE3 fusion proteins appear to induce transcriptional upregulation of MET and activation of downstream signaling, suggesting that MET may be a valid therapeutic target [41].

There is very little clinical data to help guide management of patients with advanced translocation RCCs. Choueiri and colleagues reported a retrospective analysis of 15 patients with translocation carcinoma who received anti-VEGF targeted therapy [42]. The overall response rate was 20%, with a median PFS of 7.1 months and OS of 14.3 months. A second retrospective study by Malouf and colleagues reported on 21 patients with metastatic translocation carcinoma who received VEGFR and mTOR therapy [43]. Seven patients achieved an objective response by RECIST and the median OS of the cohort was 27 months. These results suggest that VEGF-pathway antagonists may have some activity in these tumors, but prospective clinical trials are needed to further define the role of these agents.

Chromophobe RCC

Chromophobe RCC (chRCC) comprises approximately 5% of all RCC [7]. It is so named for its translucent appearance on light microscopy with H&E staining. chRCC are typically slow growing and are associated with favorable prognosis [44]. chRCC are characterized by hypodiploidy and loss of chromosomes 1,2,6,10,13,17 and 21 [45]. In addition, pathway analyses suggest dysregulation of mTOR and c-erbB2 signaling in chRCC [46]. Upregulation of KIT has also been demonstrated in chRCC. In one study, IHC staining of 29 chromophobe carcinomas demonstrated that 83% stained strongly for KIT while none of the other RCC types expressed KIT [47].

Hereditary chRCC is a feature of Birt-Hogg-Dube' (BHD) syndrome [48]. This is an autosomal dominant renal carcinoma syndrome caused by germline alterations in the *folliculin* (*FLCN*) gene, located on chromosome 17p11.2 [49–50]. *FLCN* loss has been shown to result in upregulation of the Akt-mTOR pathway both in vitro and in a conditional *FLCN* mouse knockout model [51]. In addition, *FLCN* $-/-$ mice treated with rapamycin (mTORC1 inhibitor) had longer OS and regression of the cystic kidney phenotype engendered by *FLCN* loss [51]. There is a paucity of data examining responses of chRCC to conventional targeted therapy. In one retrospective study, among 12 patients with metastatic chRCC treated with sunitinib or sorafenib, three patients had a partial response and nine had stable disease for at least 3 months [52]. Several recent case reports have also suggested that mTOR inhibitors may have activity in chRCC. Patients with metastatic chRCC are eligible for inclusion in phase II trials of everolimus versus sunitinib in non-clear cell RCC (NCT01185366, NCT01108445).

RCC Associated with Succinate Dehydrogenase Loss

Germline mutations affecting *succinate dehydrogenase subunit B* (*SDHB*) have been associated with hereditary paraganglioma and pheochromocytoma. Recently, early onset renal tumors including ccRCC, chRCC and oncocytomas were identified as part of this hereditary syndrome [53]. Loss of *SDHB* activity leads to accumulation of succinate and inhibition of prolyl hydroxylase activity with consequent stabilization of hypoxia inducible

factor and upregulation of its downstream transcriptional targets [54]. As with HLRCC associated tumors, disrupting tumor vasculature with agents such as VEGF- pathway inhibitors might provide a reasonable approach to these tumors, and are the subject of ongoing preclinical studies. To date, no clinical trials have been reported using targeted agents in patients with *SDHB* deficient tumors.

Tuberous Sclerosis

Tuberous sclerosis (TS) is an autosomal dominant disease characterized by multiple solid organ hamartomas, developmental delay, and epilepsy [55]. *TSC1* encodes hamartin and *TSC2* encodes tuberin, which form a heterodimer that acts as a GTPase-activating protein for Rheb, a Ras-family GTPase that activates mTORC1 [56]. The TSC1–TSC2 complex promotes stabilization of Rheb-GDP, and consequent inhibition of mTOR activity. TSC1-deficient and TSC2-deficient tumors exhibit increased phosphorylation of p70S6 kinase, S6 ribosomal protein and 4E-BP1, downstream effectors of mTORC1 activation, and key components in the initiation of mRNA translation and protein synthesis [57]. The tuberous sclerosis genes *TSC1* and *TSC2* are also involved in the AMPK–mTOR nutrient and energy sensing pathway [57].

Renal lesions occur in 60–80% of TSC patients and include angiomyolipomas (AML), cysts, and RCC [58]. RCC has been reported in 1–4% of TSC patients, and although the overall incidence parallels that of RCC in the general population, patients with TSC and RCC are younger (average age 28 years) [58]. Although ccRCC is the predominant malignant histologic subtype, other histologies have also been reported in this population [59].

Based on activation of the mTORC1 pathway in patients with TS, a recent multicenter phase II trial of sirolimus was undertaken in 36 patients with TSC and AML [60]. Sirolimus use was associated acceptable toxicity and resulted in an overall response rate of 44%, with 16 patients achieving a PR, and a mean decrease in renal AML size of 29%. Interestingly, although treated AMLs regrew when sirolimus was discontinued, responses tended to persist if treatment was continued [60]. To date, there are no clinical trials assessing mTOR inhibition in ccRCC or other variants in TS patients.

Conclusions

Targeted systemic therapies continue to be the mainstay for the management of metastatic RCC, although properly selected patients may greatly benefit from high dose interleukin-2. With six approved agents for ccRCC currently available, kidney cancer specialists should continue to focus their efforts on identifying logical, efficacious, and tolerable drug combinations as well as optimal drug-sequencing strategies. Mechanism-based therapeutic interventions are becoming more realistic in non-clear cell variants as we begin to unravel the diverse molecular mechanisms underlying these tumors. In addition to standard survival endpoints, symptom scores such as the FKSI and FKSI-DRS should be considered for incorporation into new trials so that disease-specific quality of life outcomes can be better understood.

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References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011; 61(2):69–90. [PubMed: 21296855]
2. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011; 61(4): 212–236. [PubMed: 21685461]
3. Altekruse, S.; Kosary, C.; Krapcho, M., et al. [cited 2010 February 25] Seer cancer statistics review, 1975–2007, national cancer institute. 2009. Available from: <http://seer.cancer.gov/statfacts/html/kidrp.html#risk>.
4. Singer EA, Bratslavsky G, Linehan WM, et al. Targeted therapies for non-clear renal cell carcinoma. *Target Oncol.* 2010; 5(2):119–129. [PubMed: 20680492]
5. Singer EA, Gupta GN, Srinivasan R. Update on targeted therapies for clear cell renal cell carcinoma. *Curr Opin Oncol.* 2011; 23(3):283–289. [PubMed: 21330923]
6. NIH. [cited 2010 November 24] Clinical trials registry. 2010. Available from: <http://clinicaltrials.gov/ct2/home>.
7. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med.* 2005; 353(23):2477–2490. [PubMed: 16339096]
8. Latif F, Tory K, Gnarr J, et al. Identification of the von hippel-lindau disease tumor suppressor gene. *Science.* 1993; 260(5112):1317–1320. [PubMed: 8493574]
9. Moore LE, Nickerson ML, Brennan P, et al. Von hippel-lindau (vhl) inactivation in sporadic clear cell renal cancer: Associations with germline vhl polymorphisms and etiologic risk factors. *PLoS Genet.* 2011; 7(10):e1002312. [PubMed: 22022277]
10. Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the swi/snf complex gene pbrm1 in renal carcinoma. *Nature.* 2011; 469(7331):539–542. [PubMed: 21248752]
11. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007; 356(2):115–124. [PubMed: 17215529]
12. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007; 356(22):2271–2281. [PubMed: 17538086]
13. Escudier B, Bellmunt J, Negrier S, et al. Phase iii trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (avoren): Final analysis of overall survival. *J Clin Oncol.* 2010; 28(13):2144–2150. [PubMed: 20368553]
14. Rini BI, Halabi S, Rosenberg JE, et al. Phase iii trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: Final results of calgb 90206. *J Clin Oncol.* 2010; 28(13):2137–2143. [PubMed: 20368558]
15. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007; 356(2):125–134. [PubMed: 17215530]
16. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : Final results and analysis of prognostic factors. *Cancer.* 2010; 116(18):4256–4265. [PubMed: 20549832]
17. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase iii trial. *J Clin Oncol.* 2010; 28(6):1061–1068. [PubMed: 20100962]
18. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase iii trial. *Lancet.* 2008; 372(9637):449–456. [PubMed: 18653228]
19. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (axis): A randomised phase 3 trial. *Lancet.* 2011
20. Cella D, Yount S, Du H, et al. Development and validation of the functional assessment of cancer therapy-kidney symptom index (fksi). *J Support Oncol.* 2006; 4(4):191–199. [PubMed: 16669463]
21. Cella D, Yount S, Brucker PS, et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. *Value Health.* 2007; 10(4):285–293. [PubMed: 17645683]

22. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the met proto-oncogene in papillary renal carcinomas. *Nat Genet.* 1997; 16(1):68–73. [PubMed: 9140397]
23. Peruzzi B, Bottaro DP. Targeting the c-met signaling pathway in cancer. *Clin Cancer Res.* 2006; 12(12):3657–3660. [PubMed: 16778093]
24. Schoffski P, Garcia JA, Stadler WM, et al. A phase ii study of the efficacy and safety of amg 102 in patients with metastatic renal cell carcinoma. *BJU Int.* 2011; 108(5):679–686. [PubMed: 21156020]
25. Srinivasan R, Choueiri TK, Vaishampayan U. A phase ii study of the dual met/vegfr2 inhibitor xl880 in patients (pts) with papillary renal carcinoma (prc). *J Clin Oncol.* 2008; 26:5103.
26. Srinivasan R, Linehan WM, Vaishampayan U. A phase ii study of two dosing regimens of gsk 1363089 (gsk089), a dual met/vegfr2 inhibitor, in patients (pts) with papillary renal carcinoma (prc). *J Clin Oncol.* 2009; 27:5103.
27. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007; 356(22):2271–2281. [PubMed: 17538086]
28. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol.* 2009; 26(2):202–209. [PubMed: 19229667]
29. Pignot G, Elie C, Conquy S, et al. Survival analysis of 130 patients with papillary renal cell carcinoma: Prognostic utility of type 1 and type 2 subclassification. *Urology.* 2007; 69(2):230–235. [PubMed: 17275070]
30. Isaacs JS, Jung YJ, Mole DR, et al. Hif overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: Novel role of fumarate in regulation of hif stability. *Cancer Cell.* 2005; 8(2):143–153. [PubMed: 16098467]
31. Sudarshan S, Sourbier C, Kong HS, et al. Fumarate hydratase deficiency in renal cancer induces glycolytic addiction and hypoxia-inducible transcription factor 1alpha stabilization by glucose-dependent generation of reactive oxygen species. *Mol Cell Biol.* 2009; 29(15):4080–4090. [PubMed: 19470762]
32. Tong WH, Sourbier C, Kovtunovych G, et al. The glycolytic shift in fumarate-hydratase-deficient kidney cancer lowers ampk levels, increases anabolic propensities and lowers cellular iron levels. *Cancer Cell.* 2011; 20(3):315–327. [PubMed: 21907923]
33. NIH. [cited 2010 November 22] A phase ii study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (hlrc) or sporadic papillary renal cell cancer. 2010. Available from: <http://clinicaltrials.gov/ct2/show/NCT01130519?term=bevacizumab+and+erlotinib&rank=2>.
34. Eble, JN.; Sauter, G.; Epstein, JI., et al. World health organization classification of tumours. Lyon, France: IARC Press; 2004. Pathology and genetics of tumours of the genitourinary system and male genital organs.
35. Argani P, Antonescu CR, Illei PB, et al. Primary renal neoplasms with the aspl-tfe3 gene fusion of alveolar soft part sarcoma: A distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. *Am J Pathol.* 2001; 159(1):179–192. [PubMed: 11438465]
36. Argani P, Hawkins A, Griffin CA, et al. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal hmb45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. *Am J Pathol.* 2001; 158(6):2089–2096. [PubMed: 11395386]
37. Ross H, Argani P. Xp11 translocation renal cell carcinoma. *Pathology.* 2010; 42(4):369–373. [PubMed: 20438411]
38. Malouf GG, Camparo P, Molinie V, et al. Transcription factor e3 and transcription factor eb renal cell carcinomas: Clinical features, biological behavior and prognostic factors. *J Urol.* 2011; 185(1):24–29. [PubMed: 21074195]
39. Hua X, Liu X, Ansari DO, et al. Synergistic cooperation of tfe3 and smad proteins in tgfbeta-induced transcription of the plasminogen activator inhibitor-1 gene. *Genes Dev.* 1998; 12(19):3084–3095. [PubMed: 9765209]

40. Argani P, Hicks J, De Marzo AM, et al. Xp11 translocation renal cell carcinoma (rcc): Extended immunohistochemical profile emphasizing novel rcc markers. *Am J Surg Pathol.* 2010; 34(9): 1295–1303. [PubMed: 20679884]
41. Tsuda M, Davis IJ, Argani P, et al. Tfe3 fusions activate met signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic met inhibition. *Cancer Res.* 2007; 67(3):919–929. [PubMed: 17283122]
42. Choueiri TK, Lim ZD, Hirsch MS, et al. Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic xp11.2 translocation renal cell carcinoma. *Cancer.* 2010; 116(22): 5219–5225. [PubMed: 20665500]
43. Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic xp11 translocation/tfe3 gene fusion renal cell carcinoma (rcc): A report from the juvenile rcc network. *Ann Oncol.* 2010; 21(9):1834–1838. [PubMed: 20154303]
44. Volpe A, Novara G, Antonelli A, et al. Chromophobe renal cell carcinoma (rcc): Oncological outcomes and prognostic factors in a large multicentre series. *BJU Int.* 2011
45. Speicher MR, Schoell B, du Manoir S, et al. Specific loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 in chromophobe renal cell carcinomas revealed by comparative genomic hybridization. *Am J Pathol.* 1994; 145(2):356–364. [PubMed: 7519827]
46. Tan MH, Wong CF, Tan HL, et al. Genomic expression and single-nucleotide polymorphism profiling discriminates chromophobe renal cell carcinoma and oncocytoma. *BMC Cancer.* 2010; 10:196. [PubMed: 20462447]
47. Pan CC, Chen PC, Chiang H. Overexpression of kit (cd117) in chromophobe renal cell carcinoma and renal oncocytoma. *Am J Clin Pathol.* 2004; 121(6):878–883. [PubMed: 15198361]
48. Pavlovich CP, Grubb RL 3rd, Hurley K, et al. Evaluation and management of renal tumors in the birt-hogg-dube syndrome. *J Urol.* 2005; 173(5):1482–1486. [PubMed: 15821464]
49. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-hogg-dube syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet.* 2001; 69(4):876–882. [PubMed: 11533913]
50. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the birt-hogg-dube syndrome. *Cancer Cell.* 2002; 2(2):157–164. [PubMed: 12204536]
51. Baba M, Furihata M, Hong SB, et al. Kidney-targeted birt-hogg-dube gene inactivation in a mouse model: Erk1/2 and akt-mtor activation, cell hyperproliferation, and polycystic kidneys. *J Natl Cancer Inst.* 2008; 100(2):140–154. [PubMed: 18182616]
52. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol.* 2008; 26(1):127–131. [PubMed: 18165647]
53. Ricketts C, Woodward ER, Killick P, et al. Germline sdhb mutations and familial renal cell carcinoma. *J Natl Cancer Inst.* 2008; 100(17):1260–1262. [PubMed: 18728283]
54. Pollard PJ, Briere JJ, Alam NA, et al. Accumulation of krebs cycle intermediates and over-expression of hif1alpha in tumours which result from germline fh and sdh mutations. *Hum Mol Genet.* 2005; 14(15):2231–2239. [PubMed: 15987702]
55. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet.* 2008; 372(9639):657–668. [PubMed: 18722871]
56. Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: A metabolic disease. *Naure Reviews Urology.* 2010 May 7. In press.
57. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med.* 2006; 355(13):1345–1356. [PubMed: 17005952]
58. Bjornsson J, Short MP, Kwiatkowski DJ, et al. Tuberous sclerosis-associated renal cell carcinoma. Clinical, pathological, and genetic features. *Am J Pathol.* 1996; 149(4):1201–1208. [PubMed: 8863669]
59. Kato I, Inayama Y, Yamanaka S, et al. Epithelioid angiomyolipoma of the kidney. *Pathol Int.* 2009; 59(1):38–43. [PubMed: 19121090]
60. Dabora SL, Franz DN, Ashwal S, et al. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: Kidney angiomyolipomas and other tumors regress and vegf- d levels decrease. *PLoS One.* 2011; 6(9):e23379. [PubMed: 21915260]

Recent findings

The treatment of advanced RCC continues to be a major challenge for uro-oncologists. The rapid growth in therapeutic options, largely targeting the VHL/HIF pathway, has brought much needed improvements in overall and progression-free survival, although durable complete responses remain elusive. The recent identification of mutations in genes involved in chromatin remodeling will likely lead to the investigation of components of this critical process as valid therapeutic targets in clear cell RCC. Similarly, efforts to decipher the molecular mechanisms underlying non-clear cell variants of RCC are beginning to engender novel therapeutic strategies directed against these rarer forms of kidney cancer. Despite the availability of multiple treatment options, several challenges remain: selecting the best first-line or subsequent therapy for a given patient, the optimal sequencing of the various agents available, designing trials with appropriate comparison arms and endpoints, and identifying safe and effective drug combinations.

Table 1

Genetic Alterations Associated with RCC

Alteration	Renal Manifestation	Gene	Chromosome
Birt-Hogg-Dube' (BHD)	Hybrid oncocytic, chromophobe, and clear cell renal cell carcinoma; oncocytoma	<i>FLCN</i>	17p11
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	Papillary renal cell carcinoma type 2	<i>FH</i>	1q42-43
Hereditary papillary renal carcinoma (HPRC)	Papillary renal cell carcinoma type 1	<i>MET</i>	7q31
Polybromo 1	Clear cell renal cell carcinoma	<i>PBRM1</i>	3p
Succinate Dehydrogenase B	Paraganglioma/pheochromocytoma Clear cell, chromophobe, oncocytoma	<i>SDH-B</i>	1p36
Translocation carcinoma	Clear cell, papillary	<i>TFE3</i> <i>TFE-B</i>	Xp11 6p21
Tuberous sclerosis	Angiomyolipoma Clear cell, chromophobe, papillary, oncocytoma	<i>TSC1</i> <i>TSC2</i>	9q34 16p13
Von Hippel-Lindau (VHL)	Clear cell renal cell carcinoma	<i>VHL</i>	3p25

Table 2

FDA-Approved Targeted Therapies for Advanced Clear Cell Renal Cell Carcinoma

Therapy	Target	Treatment Line	Comparison Arm	Primary Endpoint
Bevacizumab + IFN- α (AVOREN) [13]	VEGF	First-line	Placebo + IFN- α	OS
Bevacizumab + IFN- α (CALGB) [14]	VEGF	First-line	IFN- α	OS
Pazopanib [17]	VEGFR	First-line or Cytokine Failure	Placebo	PFS
Sorafenib [15]	VEGFR	Cytokine Failure	Placebo	OS
Sunitinib [11]	VEGFR	First-line	IFN- α	PFS
Everolimus [16]	mTOR	VEGFR Failure	Placebo	PFS
Temsirolimus [12]	mTOR	First-line	IFN- α	OS

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