Metastatic Renal Cell Cancer—Systemic Therapy

Amit Joshi¹ · Arvind Sahu¹ · Vanita Noronha¹ · Vijay Patil¹ · Kumar Prabhash¹

Received: 6 December 2017 / Accepted: 4 January 2018 / Published online: 29 January 2018
© Indian Association of Surgical Oncology 2018

Abstract

Management of metastatic renal cell carcinoma (mRCC) has evolved considerably in the past 10 years due to better understanding of tumor biology. This development has changed mRCC to a chronic progressive disease with several lines of treatment options. The introduction of several new targeted therapies including immunotherapy has improved median overall survival of approximately 1 year to >2 years in mRCC.

Keywords Metastatic RCC · Targeted therapy · Sunitinib · Pazopanib

Introduction

In the past, metastatic renal cell carcinoma (mRCC) was considered a fatal disease with limited therapeutic options. This has changed dramatically in the past 10 years due to advances in the understanding of tumor biology converting it to a chronic progressive disease with several tiers of therapeutic options. The introduction of several new targeted therapies has improved survival from a median overall survival (OS) of approximately 1 year to >2 years [1].

Eighty-five percent of all RCC are clear cell tumors and the rest include papillary, chromophobe, and oncocytoma, as well as other minor subtypes [2]. At the time of diagnosis, 20–30% of patients have metastatic disease upfront and about 20% will develop metastasis after being treated for an early-stage disease [3]. Metastatic RCC is one of the few tumors in which spontaneous tumor regressions were reported suggesting RCC to be an immunogenic tumor [4, 5]. Immune cells infiltrating the RCC tumor tissue suggested the role of the adaptive immune system leading to non-specific immunotherapy trials with interleukin-2 (IL-2) and interferon (IFN- α) [6, 7]. With response rates up to 30% and durable response rates up to 7%, immunotherapy was the only treatment option for RCC for many years [8–10]. mRCC being poorly responsive to chemotherapy thus opened up avenues for research of novel

treatments that have altered the natural course of the disease [11, 12]. This review discusses the therapeutic advances in mRCC over the last decade with focus on potential future targets for therapy.

Molecular Pathogenesis

The initial insights into the molecular pathogenesis of clear cell RCC came from studies in von Hippel–Lindau (VHL) disease. von Hippel–Lindau (VHL) disease is an inherited, autosomal dominant syndrome with variable penetrance. The VHL gene was identified in 1993 and found to be a tumor suppressor gene, which is also present in sporadic forms of RCC [13–15]. VHL is characterized by the development of cerebellar and spinal hemangioblastomas, retinal angiomas, pheochromocytomas, and renal cysts and tumors. Clear cell RCCs develop in 40 to 60% of patients with VHL disease; these tend to be multicentric and bilateral with an unusually early age of onset.

The VHL gene has been mapped to chromosome 3p25 and cloned [13]. Its gene product, pVHL, functions as a tumor suppressor protein [16].

There has been a lot of in-depth understanding of the biology that underlies the formation of VHL-associated tumors over the last two decades [16–20]. The VHL protein (pVHL) forms a stable complex with multiple other proteins including elongin B, elongin C, and cullin 2. This complex functions as an E3 ubiquitin ligase for many target proteins [hypoxia-inducible factor-1 α and 2 α (HIF-1 and HIF-2)] leading to their proteasomal degradation, thus regulating them within the cell [18–20]. HIF-1 and HIF-2 are two

✉ Kumar Prabhash
kprabhash1@gmail.com

¹ Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India

of the major proteins regulated by pVHL. Transcriptional activation by HIF requires the heterodimerization and nuclear translocation of alpha and beta subunits. The alpha subunits are sensitive to oxygen tension and act as a substrate for the pVHL protein complex. With normal oxygen tension, HIF-1 α and HIF-2 α are enzymatically hydroxylated which are then bound by the VHL protein complex and covalently linked to ubiquitin thereby rapidly being degraded by proteasomes. However during hypoxia, hydroxylation does not occur and thus failure of the VHL protein complex to bind to HIF α and HIF2 α leading to a failure of ubiquitination. As a result, the increased levels of HIF α and HIF2 α cause an increased mRNA transcription of a variety of proteins, thus inducing a physiologic angiogenic response. Loss of the sole functioning VHL allele in somatic tissues creates a situation analogous to hypoxia, despite the presence of normal oxygen tension [16, 17, 20, 21] inducing abnormal production of the factors that would be produced in conditions of physiologic hypoxia. pVHL also affects several other factors which have been implicated in the pathogenesis that are not regulated through the HIF-1 α system. These targets include matrix metalloproteinases (MMP) such as MMP1, MMP inhibitors, and atypical protein kinase C [16, 19].

The combined effect of various angiogenic factors and other growth factors creates an autocrine loop which provides the impetus for uncontrolled growth as suggested by the highly vascular CNS tumors found in VHL patients [22]. pVHL also regulates various other key intracellular processes like extracellular matrix control [23, 24], microtubule regulation [25–30], cilia centrosome cycle control [25–30], and cell cycle control [31–36] which are involved in the pathogenesis.

Treatment Strategies

IFN and IL-2 therapies consisted the backbone of systemic treatment in mRCC until 2005. The earliest evidence of these targeted agents comes from the RCTs designed in the cytokine era, most often following progression after interleukin (IL)-2 or IFN administered in the first-line setting. So, these agents were initially assessed in combination with or in comparison with cytokines to improve PFS and OS. Subsequently, the approval of VEGF/VEGFR inhibition as first-line treatment in mRCC led to the development of studies designed to assess both mTOR and VEGFR in the third-line setting following failure of either two VEGFR inhibitors or one VEGFR TKI and everolimus. Five agents were approved as a first-line agent in mRCC, and two as second-line agents over the last decade. As a result of similar efficacies with the first-line agents, selection of a first-line agent is based on toxicity profiles of individual agents as well as physician preference [Fig. 1].

Inhibitors of Vascular Endothelial Growth Factor Pathway

One of the earliest and most important agents to be approved in the treatment of renal cell carcinoma (RCC) is vascular endothelial growth factor (VEGF) pathway inhibitors. Available evidence supports the use of single-agent selective VEGF pathway inhibitors in previously untreated patients or patients who have progressed after prior therapy in advanced or metastatic RCC. In view of limited data comparing one against the others as a preferred option, the choice between them should be individualized based on patient preferences and toxicity profile. The approved agents are being discussed in the following section.

Sorafenib

In 2005, the U.S. Food and Drug Administration approved sorafenib—the first VEGF inhibitor to be approved for the treatment of patients with mRCC. Sorafenib is an orally active multikinase inhibitor. Sorafenib is a tyrosine kinase inhibitor (TKI) that targets the VEGF receptors (VEGFR), the PDGF receptor β (PDGFR β), the c-Kit protein (c-Kit), the FMS-like tyrosine kinase 3 (Flt-3), and the RET proto-oncogene, and has demonstrated inhibitory activity on cell proliferation and angiogenesis [37].

Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) was the pivotal trial that led to the approval of sorafenib as a second-line agent after cytokine failure. It was a randomized, double-blind, placebo-controlled phase III study of single-agent sorafenib in 903 cytokine-refractory patients [37]. More than 99% of patients in that trial were of MSKCC favorable or intermediate risk and the efficacy of sorafenib superior to that of placebo was noted in both risk groups. The median PFS was significantly longer in those receiving sorafenib compared with placebo (5.5 versus 2.8 months, HR 0.44, 95% CI 0.35–0.55). OS with sorafenib was not significantly prolonged compared with placebo (median 17.8 versus 15.2 months, HR 0.88, 95% CI 0.74–1.04). The primary endpoint of the study was overall survival (OS), and sorafenib failed to demonstrate superiority. However, the study allowed patients originally assigned to placebo to cross-over and receive sorafenib, potentially obscuring differences in survival. The perception that older patients may be at higher risk than younger patients of toxic effects from therapy but may obtain less clinical benefit from it may be based on the underrepresentation of older patients in clinical trials and the known toxic effects of cytotoxic chemotherapy. This was addressed in a separate analysis of the TARGET trial which suggested sorafenib to be effective in older patients (≥ 70 years), as evidenced by a significant improvement in PFS (26 versus 14 weeks with placebo) [38].

Fig. 1 Chronology of FDA approval of molecular-targeted agents in metastatic renal cell carcinoma

As a first-line agent, sorafenib was studied in a phase II trial of good- and intermediate-risk patients with previously untreated advanced RCC. Patients were randomly assigned to sorafenib (400 mg orally twice a day) or IFN α (9 million units three times per week). At progression, patients originally assigned to sorafenib were allowed to escalate the dose of sorafenib to 600 mg orally twice a day, while those who had been assigned to IFN α could be crossed over to sorafenib (400 mg twice a day). Sorafenib and IFN α had similar PFS (5.7 versus 5.6 months, HR 1.14, 95% CI 0.61–1.27) but sorafenib-treated patients had greater rates of tumor size reduction, better quality of life, and improved tolerability to dose escalation to 600 mg twice a day in patients who were tolerating 400 mg twice a day and was associated with an additional period of PFS of 4 months [39, 40]. However, additional evidence is required to determine whether this approach has a role in the management of patients with advanced RCC.

Sunitinib

Shortly after sorafenib, the FDA granted sunitinib accelerated approval in January 2006 based on responses in patients with mRCC who had failed cytokine therapy and regular approval in February 2007 for the first-line treatment of patients with advanced RCC or mRCC [41, 42]. Sunitinib is an oral multi-targeted receptor tyrosine kinase inhibitor which inhibits the

VEGF receptor TK as well as other TKs associated with the platelet-derived growth factor (PDGF) receptor, Flt-3, and c-kit oncogene [43, 44]. The trial that led to the full approval of sunitinib was a randomized phase III study that compared single-agent sunitinib with IFN- α in 750 previously untreated patients with largely good- or intermediate-prognosis metastatic clear cell RCC. Patients were randomly assigned to six-week cycles of sunitinib (50 mg daily for 4 weeks, followed by 2 weeks off) or IFN- α (9 million units three times per week). The primary endpoint was PFS, and the median was significantly longer in the sunitinib arm at 11 months than in the IFN- α arm at 5 months ($p = 0.001$) [44]. Sunitinib showed a higher objective response rate than what was seen in those treated with IFN- α (47 versus 12%; $p = 0.001$) [45]. The final survival analysis showed a marginally greater median OS time with sunitinib than with IFN- α (26.4 versus 21.8 months, respectively; $p = 0.051$). The confounding effects of crossover was accounted in an exploratory analysis and it suggested that the OS time was significantly longer with sunitinib than with IFN- α (26.4 versus 20.0 months, respectively; $p = 0.036$). In addition, a separate exploratory analysis of patients who did not receive post-study cancer treatment showed that the median OS time with sunitinib was double that with IFN α (28.1 versus 14.1 months, respectively; $p = 0.003$) [45].

A randomized trial that included 292 patients with advanced RCC compared the schedule of sunitinib, i.e., the 50-mg 4-week-on/2-week-off schedule with continuous daily

treatment (37.5 mg/day). Although continuous dosing resulted in a lower time to progression compared with the 6-week dosing schedule (median 7.1 versus 9.9 months, HR 0.77, 95% CI 0.57–1.04), there were no differences in OS (23.1 versus 23.5 months, respectively) and the rate of adverse events suggesting the standard dose schedule to be used for patients who are candidates for sunitinib [46].

Even though there is limited data available, sunitinib appears to be efficacious regardless of age. A retrospective study with over 1000 patients reported no significant differences in PFS (median 11 versus 10 months) and OS (26 versus 24 months) among patients < 70 and ≥ 70 years, respectively, when sunitinib was administered in the first-line setting [41]. In comparison to younger patients, patients 70 years and older experienced significantly more treatment-related toxicities, including fatigue (69 versus 60%), peripheral edema (27 versus 17%), and thrombocytopenia (25 versus 16%). So, the use of sunitinib among older patients should be based on considerations of the treatment-related risks and the goals and preferences of the individual patient.

Pazopanib

Pazopanib is an oral multikinase inhibitor targeting VEGF, platelet-derived growth factor (PDGF), and Kit receptors. The activity of pazopanib in mRCC evaluated in a phase 3 study in 2010 which enrolled 435 patients randomly assigned to pazopanib or placebo, all of whom had good- or intermediate-risk disease. Approximately one half were treatment-naïve and one half had received prior cytokine therapy. Pazopanib arm showed a significant increase in progression-free survival (median, 9 versus 4 months, hazard ratio [HR] for recurrence 0.46, 95% CI 0.34–0.62). This benefit was seen in both the treatment-naïve as well as the cytokine-pre-treated subpopulation [treatment-naïve arm (11.1 vs. 2.8 months) as well as the cytokine-treated arm (7.4 vs. 4.2 months)] [47]. However, the lack of benefit in overall survival in this study could be attributed to the high rate of crossover and to the use of other treatments after disease progression in patients on the placebo arm. Head-on comparison of pazopanib with sunitinib suggested pazopanib to be non-inferior to sunitinib in terms of PFS and well tolerated by patients, with significantly less fatigue, hand–foot syndrome, thrombocytopenia, and other markers of safety and quality of life as demonstrated in two randomized trials [48, 49].

Cabozantinib

Cabozantinib is a small-molecule multikinase inhibitor which targets the VEGF receptor. It also inhibits the MET and AXL genes, which are associated with a poor prognosis and the development of resistance to VEGF inhibition. The phase III METEOR trial randomized 658 previously treated mRCC

patients (progressed after receiving prior VEGF TKI therapy) to receive either cabozantinib (60 mg/day) or everolimus (10 mg/day). The interim analysis at a minimum follow-up of 11 months in the first 375 patients suggested progression-free survival to be significantly longer with cabozantinib compared with everolimus (median, 7.4 versus 3.8 months, HR 0.58, 95% CI 0.45–0.75), and there was a trend toward longer overall survival with cabozantinib compared with everolimus (HR 0.67, 95% CI 0.51–0.89). The objective response rate, based upon independent radiologic review, was also significantly higher with cabozantinib (21 versus 5%). The toxicity in patients on the cabozantinib arm was significant, with 68% of patients experiencing a grade 3 or 4 event compared to 58% in the everolimus arm. The most frequent of such events were hypertension and diarrhea (15 and 11%, respectively). Adverse events required dose reductions in 60 and 25% of patients, respectively, and discontinuation due to an adverse event occurred in 9 and 10% of patients, respectively [50].

Axitinib

Axitinib is a selective orally available inhibitor of the VEGF receptors 1, 2, and 3, as opposed to sorafenib, sunitinib, and pazopanib which have multiple targets. Axitinib demonstrated higher response rates and more toxicity than sorafenib in randomized clinical trials. However, it has not been compared with pazopanib or sunitinib in the first-line setting or with cabozantinib in the second-line setting. The AXIS study was a phase 3 RCT comparing axitinib to sorafenib in patients with mRCC that progressed despite treatment with sunitinib, bevacizumab plus IFN, temsirolimus, or cytokines. Median PFS was superior with axitinib compared to sorafenib (8.3 versus 5.7 months) [51, 52]. This improved PFS seen in the second-line setting axitinib led to its evaluation as a first-line agent in a multicenter randomized trial in which 288 patients were randomly assigned to treatment with axitinib (5 mg twice a day) or sorafenib (400 mg twice a day). Axitinib resulted in a trend toward improved PFS (10 versus 6.5 months, HR 0.77, 95% CI 0.56–1.05) and a higher ORR (32 versus 15%) with higher rates of toxicity, including diarrhea (50 versus 40%), hypertension (49 versus 29%), weight loss (37 versus 24%), fatigue (33 versus 26%), and anorexia (29 versus 19%) [53].

Inhibitors of mTOR Pathway

Temsirolimus

After the success of sorafenib and sunitinib, temsirolimus, an mTOR inhibitor, was also approved for mRCC in 2007. In a phase III trial, 626 previously untreated patients were randomly assigned to temsirolimus, temsirolimus plus interferon-α (IFNα), or IFNα monotherapy. Most patients had three out of six poor prognostic factors and only 80% of patients enrolled

had ccRCC, which is a different patient population than most other studies. Temsirolimus significantly prolonged the median overall survival compared with IFNa as a single agent (10.9 versus 7.3 months, hazard ratio [HR] for mortality 0.73, 95% CI 0.58–0.92). There was no additional benefit from combining temsirolimus with IFNa [54]. BEST trial (E2804) of 361 patients who had not received prior targeted therapy in which the patients were randomly assigned to bevacizumab as a single agent, bevacizumab plus temsirolimus, bevacizumab plus sorafenib, or sorafenib plus temsirolimus showed none of the combination regimens to be better compared with bevacizumab monotherapy. Rather, the two combinations incorporating temsirolimus had a worse therapeutic index compared with bevacizumab monotherapy [55]. As a second-line agent as in the INTORSECT trial of 512 patients who had progressed on sunitinib, temsirolimus was less active than sorafenib with overall survival being shorter (median, 12.3 versus 16.6 months, HR 1.31, 95% CI 1.05–1.63) [56].

Everolimus

Everolimus is an orally administered mTOR inhibitor. Although everolimus has activity in patients with advanced RCC, randomized trials using active rather than placebo comparators have not established a role as either initial therapy or second-line therapy. RECORD-3 trial which randomized 471 previously untreated patients to either everolimus or sunitinib showed PFS—the primary endpoint to be worse with everolimus (7.9 versus 10.7 months, HR 1.4, 95% CI 1.2–1.8). Overall progression-free survival after crossover to sunitinib following everolimus was inferior to sunitinib followed by everolimus (21.1 versus 25.8 months) [57].

Immunotherapy of Renal Cell Carcinoma

Since the time William Coley reported that an injection of killed bacteria into sites of sarcoma could lead to tumor shrinkage, significant advances in the understanding of the relationship between immune surveillance and tumor growth and development have been made. Removal of primary renal cell carcinomas (RCCs) can evoke an immune response that occasionally results in spontaneous and dramatic remissions in metastases, particularly in the lung. These observations were followed by the clinical demonstration of antitumor activity with the cytokine interleukin-2 (IL-2) and interferon- α (IFNa), although only a minority of patients derived major clinical benefit.

Immunotherapy with monoclonal antibodies directed against the programmed cell death 1 (PD-1) protein has become an integral part of the management of advanced melanoma and non-small cell lung cancer, and these findings are now being extended to a large number of other malignancies, including advanced RCC.

High-dose bolus IL-2 remains an option for carefully selected favorable-prognosis patients with access to this form of therapy. Nivolumab has an established role for patients who had been treated with a vascular endothelial growth factor (VEGF) receptor inhibitor regardless of whether they had received high-dose IL-2. Additional trials with nivolumab and other checkpoint inhibitors are extending these findings and will be required to define the optimal way to integrate these agents into patient management.

Nivolumab and Checkpoint Inhibition Nivolumab is an anti-programmed cell death-1 (PD-1) antibody that has received regulatory approval for patients with advanced melanoma and non-small cell lung cancer based upon a demonstration of improved overall survival. CheckMate 025 trial—a phase III trial which randomized 821 patients to nivolumab (3 mg/kg every 2 weeks) or everolimus (10 mg/day) and all patients had received one or two prior anti-angiogenic therapies (72 and 28%, respectively) with sunitinib, pazopanib, or axitinib (59, 30, and 12%, respectively). The trial was stopped early based upon improved overall survival in a planned interim analysis. With a minimum follow-up of 13 months, the OS was significantly increased with nivolumab compared with everolimus (median, 25.0 versus 21.8 months, hazard ratio [HR] 0.73, 95% CI 0.57–0.93) with no difference in PFS (median, 4.6 versus 4.4 months, HR 0.88, 95% CI 0.75–1.03). There was less grade 3 or 4 toxicity with nivolumab compared with everolimus (19 versus 37%). The most frequent adverse event in patients treated with nivolumab was fatigue, which was present in 33% of patients, but was severe (grade 3 or 4) in only 2% of cases. The most frequent adverse event with everolimus was fatigue (88%), and the most frequent grade 3 or 4 toxicity was anemia (8% of cases). Expression of the PD-1 ligand 1 (PD-L1) on tumor cells was not associated with benefit to nivolumab, and those with $\geq 1\%$ expression and those with $< 1\%$ expression had a similar benefit compared with everolimus [58].

Pembrolizumab

Pembrolizumab is another PD-1-targeted antibody that has received regulatory approval in patients with advanced melanoma. There are two randomized phase II trials are being conducted in patients with advanced RCC to determine whether pembrolizumab has a role in patients with advanced RCC—one (NCT02089685), pembrolizumab is being evaluated alone and in combination with pegylated interferon- α (IFNa) and, in the other (NCT02014636), pembrolizumab is being studied alone and in combination with pazopanib.

Atezolizumab

Atezolizumab, a monoclonal antibody that targets the PD-1 ligand, has also demonstrated activity in patients with advanced

RCC and is undergoing further development. A phase II trial (NCT01984242) randomly assigned 305 previously untreated patients with locally advanced or metastatic RCC to one of three arms: atezolizumab with or without bevacizumab versus sunitinib with crossover from the single-agent arms to the combination of atezolizumab plus bevacizumab permitted at time of progression, the results of which are awaited. A phase III study of atezolizumab and bevacizumab compared with sunitinib in previously untreated metastatic RCC patients is underway to evaluate the clinical efficacy of this combination in the first-line setting (NCT02420821).

Conclusions

The advent of targeted therapies in mRCC has revolutionized the management of the disease and improved the outlook for patients. With the current generation of VEGFR TKIs and mTOR inhibitors, a plateau in terms of PFS and OS has been achieved. Despite several attempts, combination therapy of currently approved targeted drugs did not benefit in comparison with single agent. Therefore, there is a need to sequence available agents properly and to integrate the novel agents under development to meet the challenge of improving survival in mRCC.

References

- Escudier B, Eisen T, Porta C, Patard JJ, Khoo V, Algaba F et al (2012) Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 23(suppl 7): vii65–vii71
- Karumanchi SA, Merchan J, Sukhatme VP (2002) Renal cancer: molecular mechanisms and newer therapeutic options. *Curr Opin Nephrol Hypertens* 11(1):37–42
- Ljungberg B, Campbell SC, Choi HY, Cho HY, Jacqmin D, Lee JE et al (2011) The epidemiology of renal cell carcinoma. *Eur Urol* 60(4):615–621. <https://doi.org/10.1016/j.eururo.2011.06.049>
- Lekanidi K, Vlachou PA, Morgan B, Vasanthan S (2007) Spontaneous regression of metastatic renal cell carcinoma: case report. *J Med Case Rep* 1(1):89. <https://doi.org/10.1186/1752-1947-1-89>
- Lokich J (1997) Spontaneous regression of metastatic renal cancer. Case report and literature review. *Am J Clin Oncol* 20(4):416–418. <https://doi.org/10.1097/00000421-199708000-00020>
- Attig S, Hennenlotter J, Pawelec G, Klein G, Koch SD, Pircher H, Feyerabend S, Wernet D, Stenzl A, Rammensee HG, Gouttefangeas C (2009) Simultaneous infiltration of polyfunctional effector and suppressor T cells into renal cell carcinomas. *Cancer Res* 69(21): 8412–8419. <https://doi.org/10.1158/0008-5472.CAN-09-0852>
- Schendel DJ, Gansbacher B, Oberneder R, Kriegmair M, Hofstetter A, Riethmüller G et al (1993) Tumor-specific lysis of human renal cell carcinomas by tumor-infiltrating lymphocytes. I. HLA-A2-restricted recognition of autologous and allogeneic tumor lines. *J Immunol Baltim Md* 150(8):4209–4220
- Fisher RI, Rosenberg SA, Fyfe G (2000) Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 6(Suppl 1):S55–S57
- Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH, White DE (1994) Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA* 271(12):907–913. <https://doi.org/10.1001/jama.1994.03510360033032>
- Sd F (2000) Interferon in metastatic renal cell carcinoma. *Semin Oncol* 27(2):187–193
- Rj A (2000) Chemotherapy for renal cell carcinoma. *Semin Oncol* 27(2):177–186
- Yagoda A, Petrylak D, Thompson S (1993) Cytotoxic chemotherapy for advanced renal cell carcinoma. *Urol Clin North Am* 20(2): 303–321
- Latif F, Tory K, Gnarr J, Yao M, Duh FM, Orcutt ML et al (1993) Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 260(5112):1317–1320. <https://doi.org/10.1126/science.8493574>
- Maher ER, Neumann HP, von Richard S (2011) Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet* 19(6): 617–623. <https://doi.org/10.1038/ejhg.2010.175>
- Leung SK, Ohh M (2002) Playing tag with HIF: the VHL story. *J Biomed Biotechnol* 2(3):131–135. <https://doi.org/10.1155/S110724302205057>
- Kim WY, Kaelin WG (2004) Role of VHL gene mutation in human cancer. *J Clin Oncol Off J Am Soc Clin Oncol* 22(24):4991–5004. <https://doi.org/10.1200/JCO.2004.05.061>
- Pugh CW, Ratcliffe PJ (2003) Regulation of angiogenesis by hypoxia: role of the HIF system. *Nat Med* 9(6):677–684. <https://doi.org/10.1038/nm0603-677>
- Kaelin WG (2002) Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer* 2(9):673–682. <https://doi.org/10.1038/nrc885>
- Sufan RI, Jewett MAS, Ohh M (2004) The role of von Hippel-Lindau tumor suppressor protein and hypoxia in renal clear cell carcinoma. *Am J Physiol Renal Physiol* 287(1):F1–F6. <https://doi.org/10.1152/ajprenal.00424.2003>
- Barry RE, Krek W (2004) The von Hippel-Lindau tumour suppressor: a multi-faceted inhibitor of tumorigenesis. *Trends Mol Med* 10(9):466–472. <https://doi.org/10.1016/j.molmed.2004.07.008>
- Maxwell PH, Pugh CW, Ratcliffe PJ (2001) Activation of the HIF pathway in cancer. *Curr Opin Genet Dev* 11(3):293–299
- de Paulsen N, Brychzy A, Fournier MC, Klausner RD, Gnarr JR, Pause A et al (2001) Role of transforming growth factor- α in von Hippel-Lindau (VHL)(-/-) clear cell renal carcinoma cell proliferation: a possible mechanism coupling VHL tumor suppressor inactivation and tumorigenesis. *Proc Natl Acad Sci U S A* 98(4): 1387–1392
- Lolkema MP, Gervais ML, Snijckers CM, Hill RP, Giles RH, Voest EE, Ohh M (2005) Tumor suppression by the von Hippel-Lindau protein requires phosphorylation of the acidic domain. *J Biol Chem* 280(23):22205–22211. <https://doi.org/10.1074/jbc.M503220200>
- Kurban G, Hudon V, Duplan E, Ohh M, Pause A (2006) Characterization of a von Hippel Lindau pathway involved in extracellular matrix remodeling, cell invasion, and angiogenesis. *Cancer Res* 66(3):1313–1319. <https://doi.org/10.1158/0008-5472.CAN-05-2560>
- Simons M, Walz G (2006) Polycystic kidney disease: cell division without a c(lue)? *Kidney Int* 70(5):854–864. <https://doi.org/10.1038/sj.ki.5001534>
- Thoma CR, Frew IJ, Hoerner CR, Montani M, Moch H, Krek W (2007) pVHL and GSK3 β are components of a primary cilium-maintenance signalling network. *Nat Cell Biol* 9(5):588–595. <https://doi.org/10.1038/ncb1579>

27. Frew IJ, Thoma CR, Georgiev S, Minola A, Hitz M, Montani M, Moch H, Krek W (2008) pVHL and PTEN tumour suppressor proteins cooperatively suppress kidney cyst formation. *EMBO J* 27(12):1747–1757. <https://doi.org/10.1038/emboj.2008.96>
28. Hergovich A, Lisztwan J, Barry R, Ballschmieter P, Krek W (2003) Regulation of microtubule stability by the von Hippel-Lindau tumour suppressor protein pVHL. *Nat Cell Biol* 5(1):64–70. <https://doi.org/10.1038/ncb899>
29. Hergovich A, Lisztwan J, Thoma CR, Wirbelauer C, Barry RE, Krek W (2006) Priming-dependent phosphorylation and regulation of the tumor suppressor pVHL by glycogen synthase kinase 3. *Mol Cell Biol* 26(15):5784–5796. <https://doi.org/10.1128/MCB.00232-06>
30. Thoma CR, Toso A, Gutbrodt KL, Reggi SP, Frew IJ, Schraml P, Hergovich A, Moch H, Meraldi P, Krek W (2009) VHL loss causes spindle misorientation and chromosome instability. *Nat Cell Biol* 11(8):994–1001. <https://doi.org/10.1038/ncb1912>
31. Pause A, Lee S, Lonergan KM, Klausner RD (1998) The von Hippel-Lindau tumor suppressor gene is required for cell cycle exit upon serum withdrawal. *Proc Natl Acad Sci U S A* 95(3):993–998. <https://doi.org/10.1073/pnas.95.3.993>
32. Kim J, Jonasch E, Alexander A, Short JD, Cai S, Wen S et al (2009) Cytoplasmic sequestration of p27 via AKT phosphorylation in renal cell carcinoma. *Clin Cancer Res Off J Am Assoc Cancer Res* 15(1): 81–90
33. Roe J-S, Kim H-R, Hwang I-Y, Cho E-J, Youn H-D (2011) von Hippel-Lindau protein promotes Skp2 destabilization on DNA damage. *Oncogene* 30(28):3127–3138. <https://doi.org/10.1038/onc.2011.40>
34. Roe J-S, Kim H, Lee S-M, Kim S-T, Cho E-J, Youn H-D (2006) p53 stabilization and transactivation by a von Hippel-Lindau protein. *Mol Cell* 22(3):395–405. <https://doi.org/10.1016/j.molcel.2006.04.006>
35. Lai Y, Song M, Hakala K, Weintraub ST, Shiio Y (2011) Proteomic dissection of the von Hippel-Lindau (VHL) interactome. *J Proteome Res* 10(11):5175–5182. <https://doi.org/10.1021/pr200642c>
36. Li M, Fang X, Baker DJ, Guo L, Gao X, Wei Z, Han S, van Deursen JM, Zhang P (2010) The ATM-p53 pathway suppresses aneuploidy-induced tumorigenesis. *Proc Natl Acad Sci U S A* 107(32):14188–14193. <https://doi.org/10.1073/pnas.1005960107>
37. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreauc C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM, TARGET Study Group (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356(2):125–134. <https://doi.org/10.1056/NEJMoa060655>
38. Eisen T, Oudard S, Szczylik C, Gravis G, Heinzer H, Middleton R, Cihon F, Anderson S, Shah S, Bukowski R, Escudier B, for the TARGET Study Group (2008) Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. *J Natl Cancer Inst* 100(20):1454–1463. <https://doi.org/10.1093/jnci/djn319>
39. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, Negrier S, Laferriere N, Scheuring UJ, Cella D, Shah S, Bukowski RM (2009) Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 27(8):1280–1289. <https://doi.org/10.1200/JCO.2008.19.3342>
40. Amato R, Zhai J, Willis J, Saxena S, DeFoe MA (2012) Phase II trial of inpatient dose-escalated sorafenib in patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer* 10(3):153–158
41. Hutson TE (2011) Targeted therapies for the treatment of metastatic renal cell carcinoma: clinical evidence. *Oncologist* 16(Suppl 2):14–22. <https://doi.org/10.1634/theoncologist.2011-S2-14>
42. Logan JE, Rampersaud EN, Sonn GA, Chamie K, Belldgrun AS, Pantuck AJ, Slamon DJ, Kabbinnar FF (2012) Systemic therapy for metastatic renal cell carcinoma: a review and update. *Rev Urol* 14(3–4):65–78
43. Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM (2003) SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Mol Cancer Ther* 2(5):471–478
44. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 356(2): 115–124. <https://doi.org/10.1056/NEJMoa065044>
45. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 27(22):3584–3590. <https://doi.org/10.1200/JCO.2008.20.1293>
46. Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, Wilding G, Agarwal N, Thompson JA, Cella D, Bello A, Korytowsky B, Yuan J, Valota O, Martell B, Hariharan S, Figlin RA (2012) Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 30(12):1371–1377. <https://doi.org/10.1200/JCO.2011.36.4133>
47. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarbá JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE (2010) Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol Off J Am Soc Clin Oncol* 28(6):1061–1068. <https://doi.org/10.1200/JCO.2009.23.9764>
48. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, de Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK (2013) Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 369(8):722–731. <https://doi.org/10.1056/NEJMoa1303989>
49. Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg CN, Gschwend JE, de Giorgi U, Parikh O, Hawkins R, Sevin E, Négrier S, Khan S, Diaz J, Redhu S, Mehmud F, Cella D (2014) Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *J Clin Oncol Off J Am Soc Clin Oncol* 32(14):1412–1418. <https://doi.org/10.1200/JCO.2013.50.8267>
50. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, Hammers H, Hutson TE, Lee JL, Peltola K, Roth BJ, Bjarnason GA, Géczi L, Keam B, Maroto P, Heng DY, Schmidinger M, Kantoff PW, Borgman-Hagey A, Hessel C, Scheffold C, Schwab GM, Tannir NM, Motzer RJ, METEOR Investigators (2015) Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 373(19):1814–1823. <https://doi.org/10.1056/NEJMoa1510016>
51. Rini BI, Melichar B, Ueda T, Grünwald V, Fishman MN, Arranz JA, Bair AH, Pithavala YK, Andrews GI, Pavlov D, Kim S, Jonasch E (2013) Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol* 14(12):1233–1242. [https://doi.org/10.1016/S1470-2045\(13\)70464-9](https://doi.org/10.1016/S1470-2045(13)70464-9)
52. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, Oudard S, Gore ME, Tarazi J, Hariharan S, Chen C, Rosbrook B, Kim S, Rini BI (2013) Axitinib versus sorafenib as

- second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 14(6):552–562. [https://doi.org/10.1016/S1470-2045\(13\)70093-7](https://doi.org/10.1016/S1470-2045(13)70093-7)
53. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, Rosbrook B, Chen C, Kim S, Vogelzang NJ (2013) Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol* 14(13):1287–1294. [https://doi.org/10.1016/S1470-2045\(13\)70465-0](https://doi.org/10.1016/S1470-2045(13)70465-0)
 54. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lesovoy V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S, Moore L, Motzer RJ, Global ARCC Trial (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 356(22):2271–2281. <https://doi.org/10.1056/NEJMoa066838>
 55. Flaherty KT, Manola JB, Pins M, McDermott DF, Atkins MB, Dutcher JJ et al (2015) BEST: a randomized phase II study of vascular endothelial growth factor, RAF kinase, and mammalian target of rapamycin combination targeted therapy with bevacizumab, sorafenib, and temsirolimus in advanced renal cell carcinoma—a trial of the ECOG-ACRIN Cancer Research Group (E2804). *J Clin Oncol Off J Am Soc Clin Oncol* 33(21):2384–2391
 56. Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, Senico P, Niethammer A, Lu DR, Hariharan S, Motzer RJ (2014) Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 32(8):760–767. <https://doi.org/10.1200/JCO.2013.50.3961>
 57. Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, Srimuninnimit V, Pittman K, Sabbatini R, Rha SY, Flaig TW, Page R, Bavbek S, Beck JT, Patel P, Cheung F, Yadav S, Schiff EM, Wang X, Niolat J, Sellami D, Anak O, Knox JJ (2014) Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 32(25):2765–2772. <https://doi.org/10.1200/JCO.2013.54.6911>
 58. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P, CheckMate 025 Investigators (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 373(19):1803–1813. <https://doi.org/10.1056/NEJMoa1510665>