Novel agents in renal carcinoma: a reality check

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Abstract: The discovery of the molecular mechanisms underlying development of renal cell carcinoma have allowed for the development of novel targeted therapy for treatment of this disease. Recently, multiple agents have become approved by regulatory authorities for the treatment of advanced renal cell carcinoma, including sunitinib, sorafenib, bevacizumab (with interferon alpha), pazopanib, temsirolimus and everolimus. While these therapies have generated excitement and have clearly altered the treatment paradigm, multiple limitations have been elucidated over time. These include but are not limited to the fact that treatment is not associated with complete responses, a significant number of patients are primarily refractory to treatment, and clinical trials mostly include clear cell histology. Furthermore, the role of these therapies in the treatment of brain metastases remains unclear and therapies can have considerable toxicities. RECIST criteria (Response Evaluation Criteria In Solid Tumors) can be inadequate for the assessment of these modalities' treatment efficacy, and biomarkers predictive of individual patient benefit have been elusive. This review summarizes the major clinical data and discusses these limitations.

Keywords: bevacizumab, everolimus, pazopanib, renal carcinoma, sorafenib, sunitinib, targeted therapy, temsirolimus

Introduction

The incidence of renal cell carcinoma (RCC) has steadily been increasing, and was projected to account for 3.8% of adult malignancies in 2010 [Jemal *et al.* 2010]. Although it is being diagnosed earlier due to more frequent imaging, one third of patients with RCC still present at advanced stages of disease, and up to 40% of patients who undergo surgical resection will have disease recurrence [Janzen *et al.* 2003, 2010]. Systemic therapy for the treatment of metastatic renal cell carcinoma (mRCC) was previously restricted to interleukin-2 (IL-2) and interferon-α (IFN-α), as mRCC is chiefly resistant to chemotherapy [Oudard *et al.* 2007]. These cytokines are associated with high toxicity and low response rates in the first-line setting, with even fewer responses and comparable toxicity as second-line agents [Escudier *et al.* 1999; Oudard *et al.* 2007]. Understanding of abnormal signal transduction in RCC has enabled the identification, and subsequent development, of molecular targets. For example, identification that biallelic loss of the von Hippel Lindau (VHL) tumor suppressor gene leads to upregulated transcription of platelet derived growth factor (PDGF), tumor growth factor alpha (TGF-α) and vascular endothelial growth factor (VEGF), all major factors in RCC tumorigenesis, and has led to the development of several targeted therapeutic molecules that have been approved for use in advanced and metastatic RCC, including sorafenib, bevacizumab (with IFN-α), sunitinib, temsirolimus, everolimus and pazopanib [Hutson, 2011] (Table 1). The enthusiasm resulting from the initial approval of targeted therapy upon a previous landscape of nihilism has lessened somewhat recently. The realization of the noncurative nature of these compounds with sometimes significant toxicity has led to several therapeutic challenges. This review briefly outlines the data for targeted therapy in metastatic RCC and the significant challenges moving forward.

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Table 1. Efficacy of approved targeted therapies for the front-line treatment of mRCC.

Agent(s) used [Reference]	Patient population	Previous treatment	Comparator	PFS *versus* comparator (months)		OS *versus* comparator (months)		ORR *versus* comparator (%)
				Median	HR (95% CI)	Median	HR (95% CI)	
Sorafenib [Escudier *et al.* 2007b]	Clear cell mRCC	One prior treatment	Placebo	5.5 *versus* 2.8	0.44 (0.35–0.55)	17.8 *versus* 15.2	0.88 (0.74–1.04)	10 *versus* 2
Sunitinib [Motzer *et al.* 2007]	Clear cell mRCC	No prior systemic therapy	IFN-α	11 *versus* 5	0.42 (0.32–0.54)	26.4 *versus* 21.8	0.818 (0.669–0.999)	47 *versus* 12
Bevacizumab + IFN-α (AVOREN) [Escudier *et al.* 2007b]	Clear cell mRCC	No prior systemic therapy	IFN-α + placebo	10.2 *versus* 5.4	0.63 (0.52–0.75)	23.3 *versus* 21.3	0.91 (0.76–1.10)	31 *versus* 13
Bevacizumab + IFN-α (CALGB 90206) [Rini *et al.* 2008]	Clear cell mRCC	No prior systemic therapy	IFN-α	8.5 *versus* 5.2	0.71 (0.61–0.83)	18.3 *versus* 17.4	0.86 (0.73–1.01)	26 *versus* 13
Pazopanib [Sternberg *et al.* 2010]	Clear cell mRCC	+/- prior cytokine based systemic treatment	IFN-α	9.2 *versus* 4.2	0.46 (0.34–0.62)	Not reached	Not reached	30 *versus* 3
Temsirolimus [Hudes *et al.* 2007]	80% clear cell mRCC, 20% 'other' mRCC	No prior systemic therapy	Placebo	3.8 *versus* 1.9	NR	10.9 *versus* 7.3	0.73 (0.58–0.92)	8.6 *versus* 4.8
Everolimus [Motzer *et al.* 2008]	91% clear cell mRCC, 9% predominantly clear cell	Prior VEGFR TKI treatment	Placebo	4.9 *versus* 1.9	0.33 (0.25–0.45)	14.8 *versus* 14.4	0.87 (0.65–1.17)	1.8 *versus* 0

mRCC, metastatic renal cell carcinoma; CI, confidence interval; IFN, interferon; HR, hazard ratio; PD, progressive disease; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; NR, not reported; VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor.

Currently approved agents

Anti-VEGF monoclonal antibody: bevacizumab (+IFN-α)

Bevacizumab is an anti-VEGF monoclonal antibody which binds and neutralizes circulating VEGF. In 2009, intravenously administered bevacizumab in combination with subcutaneous IFN-α was approved as first-line treatment for advanced and mRCC. Two trials contributed to this combination's approval. Importantly, both assessed the same dose of bevacizumab and IFN-α. AVOREN was a randomized, double-blind study of bevacizumab plus IFN-α compared with placebo and IFN-α [Escudier *et al.* 2010; Escudier *et al.* 2007b]. CALGB 90206 was a randomized open-label study that compared bevacizumab and IFN-α with IFN-α alone [Rini *et al.* 2008, 2010]. Interim analysis of both AVOREN and CALGB 90206 showed a significantly longer progression-free survival (PFS) with the combination of bevacizumab and IFN-α compared with placebo and IFN-α, or IFN-α alone [Escudier *et al.* 2007b; Rini *et al.* 2008]. In AVOREN, PFS with bevacizumab plus IFN was 10.2 months *versus* 5.4 months in the placebo and IFN-α arm ($p = 0.001$) [Escudier *et al.* 2007b]. In CALGB, PFS was 8.5 months with bevacizumab plus IFN *versus* 5.2 months with IFN-α alone ($p < 0.0001$) [Rini *et al.* 2008]. Neither trial showed statistically significantly longer overall survival (OS) time, although data in both trials showed a numerically longer OS with bevacizumab [Escudier *et al.* 2010; Rini *et al.* 2010]. This may be partly due to confounding: in AVOREN, patients in the placebo and IFN-α arm were allowed to cross over to the double treatment group. Furthermore, the majority of patients in AVOREN who discontinued the trial received subsequent treatment [Escudier *et al.* 2010]. In CALGB 90206, while crossover was not allowed, posttrial analysis revealed that most patients in the IFN-α only arm received subsequent treatment [Rini *et al.* 2010].

VEGFR tyrosine kinase inhibitors

Sorafenib. Sorafenib is an oral multikinase inhibitor, targeting signaling by VEGFRs, PDGFRs and Ras. TARGET was a randomized, double-blind, phase III study of sorafenib treatment in patients who were refractory to cytokine therapy [Escudier *et al.* 2007a]. Initial analysis of PFS was significantly prolonged with sorafenib in comparison with placebo (5.5 months *versus* 2.8 months, $p < 0.001$), regardless of Memorial Sloan Kettering Cancer Center (MSKCC) risk score, age, prior treatment or presence of metastases. Therefore, patients in the placebo group were allowed to cross over to the sorafenib arm. At the final analysis, median OS was 17.8 months with sorafenib and 15.2 months with placebo, but this did not reach statistical significance [Escudier *et al.* 2009]. In an analysis that accounted for crossover effects, however, median OS was significantly longer in the sorafenib group compared to placebo (17.8 month *versus* 14.3 months, $p = 0.0287$) [Escudier *et al.* 2009]. Sorafenib was approved by the United States Federal Drug Administration (FDA) for the treatment of advanced mRCC in December 2005.

Sunitinib. Sunitinib, like sorafenib, is an oral receptor tyrosine kinase inhibitor (TKI) that targets signaling by PDGFRs, VEGFRs and c-kit. A randomized phase III trial compared sunitinib with IFN-α in patients with previously untreated mRCC. PFS was the primary endpoint, and it was significantly longer with sunitinib than IFN-α (11 months *versus* 5 months, $p < 0.001$), regardless of MSKCC risk score, age or sex [Motzer *et al.* 2007]. The superior PFS in the sunitinib arm allowed patients with progression of disease (PD) on IFN-α to crossover to the sunitinib arm. While second analysis revealed a statistically insignificant improvement in OS with sunitinib, (26.4 months *versus* 21.8 months, $p = 0.051$) [Motzer *et al.* 2009b], an analysis that accounted for crossover effects revealed significantly prolonged OS with sunitinib, compared with IFN-α (26.4 months *versus* 20.0 months, $p = 0.036$). Further analysis revealed that patients who did not receive treatment following the conclusion of the trial had double the median OS in the sunitinib group, compared with IFN-α (28.1 months *versus* 14.1 months, $p = 0.003$) [Motzer *et al.* 2009b]. At the second analysis, objective response rate (ORR) was 31% with sunitinib and 6% with IFN-α ($p < 0.001$), and 47% and 12%, respectively (investigator review), at the final analysis ($p < 0.001$) [Motzer *et al.* 2007, 2009b]. Importantly, quality of life (QOL) was superior in the sunitinib group ($p < 0.001$) [Motzer *et al.* 2007]. It was fully approved by the FDA in February 2007.

Pazopanib. Pazopanib is an oral angiogenesis inhibitor that targets signaling by PDGFRs, VEGFRs and c-kit. A randomized, double-blind, placebo-controlled phase III trial assessed monotherapy with pazopanib in treatment naïve

patients, or patients who had been pretreated with cytokine therapy [Sternberg *et al.* 2010]. The trial's primary endpoint was PFS, and patients who progressed on placebo were allowed to cross over into the pazopanib arm. The entire patient population that was treated with pazopanib had significantly prolonged PFS compared with those who received placebo (9.2 months *versus* 4.2 months, $p < 0.0001$), regardless of whether they were treatment naïve or had been pretreated with cytokine therapy [Sternberg *et al.* 2010]. Treatment with pazopanib significantly prolonged PFS regardless of age, sex, performance status or MSKCC score [Sternberg *et al.* 2010]. It was approved by the FDA in 2009 as a treatment for patients with advanced RCC [Sternberg *et al.* 2010].

mTOR inhibitors

Temsirolimus. Temsirolimus, an mTOR (mammalian target of rapamycin) inhibitor, was assessed in a randomized phase III study of patients with newly diagnosed mRCC and at least three predictors of short survival. The primary endpoint of OS compared temsirolimus or temsirolimus plus IFN-α with IFN-α alone in patients with mRCC and poor prognosis. Temsirolimus alone compared with IFN-α alone significantly prolonged OS (10.9 months *versus* 7.3 months, $p = 0.008$), and combination therapy with temsirolimus and IFN-α did not prolong OS compared with IFN-α alone (8.4 months *versus* 7.3 months) [Hudes *et al.* 2007]. The median PFS interval was 3.8 months with temsirolimus monotherapy, 1.9 months with IFN-α monotherapy, and 3.7 months with the combination of both [Hudes *et al.* 2007]. ORR was 8.6% with temsirolimus monotherapy, 4.8% with IFN-α alone, and 8.1% with the combination. Temsirolimus was approved for advanced RCC in 2007. This agent is the only one to show prolonged OS, and not just PFS, in a phase III trial. It is likely that such poor-prognosis patients upon progression did not receive subsequent active therapy, and thus an OS benefit was able to be shown.

Everolimus. Everolimus is an orally administered mTOR inhibitor that was FDA approved in 2009 for the treatment of advanced RCC in patients who had failed treatment with sorafenib or sunitinib [Hutson, 2011]. The RECORD-1 trial, a randomized, double-blind, placebo-controlled phase III trial compared everolimus monotherapy with placebo in patients with mRCC, who had disease progression despite VEGR TKI treatment [Motzer *et al.* 2008]. Patients who had disease progression on placebo were allowed to cross over to the everolimus treatment group. The primary endpoint was PFS, and secondary endpoints included OS and ORR. Median PFS was significantly longer with everolimus than with placebo (4.0 months *versus* 1.9 months, $p < 0.0001$), and the double-blind phase of the trial was therefore terminated early [Motzer *et al.* 2008]. Moreover, PFS was significantly prolonged with everolimus, regardless of age, sex, MSKCC risk score, or previous treatment. The study was subsequently unblinded and all patients in the placebo group were then offered everolimus therapy [Motzer *et al.* 2008]. Final analysis in 2010 revealed that median PFS was 4.9 months with everolimus *versus* 1.9 months with placebo ($p < 0.001$) [Motzer *et al.* 2010]. Median OS was 14.8 months with everolimus *versus* 14.4 months with placebo ($p = 0.162$), and 80% of patients in the placebo arm crossed over to everolimus. Correcting for crossover, survival was 1.9 times longer (95% confidence interval [CI] 0.5–8.5) with everolimus compared with placebo only [Motzer *et al.* 2010].

Challenges facing the field

Complete responses are rare

In the pivotal sorafenib trial, among 451 patients in the sorafenib group who were eligible for evaluation of best response by investigators, one patient had a complete response (CR) (<1%) [Escudier *et al.* 2007a] (Table 2). Similarly, in the sunitinib trial that led to full FDA approval, investigator assessment revealed that of 374 patients in the sunitinib arm, 11 patients had CR (2.9%) [Motzer *et al.* 2007]. In the pazopanib trial, of 390 patients, one CR was reported by independent assessment [Sternberg *et al.* 2010]. In the AVOREN trial, of 306 eligible patients in the bevacizumab plus interferon arm, four patients had CR (1%) [Escudier *et al.* 2007b]. In the CALGB 90206 trial, of 355 evaluable patients in the bevacizumab plus interferon group, two patients (<1%) achieved CR [Rini *et al.* 2008]. No CRs were reported in either of the mTOR inhibitor trials [Hudes *et al.* 2007; Motzer *et al.* 2008] (Table 2). While all of the aforementioned trials signify an important addition to the armamentarium of RCC treatment, CRs are achieved by a small percentage patients (with durability of response

Table 2. Summary of patient outcomes to therapy.

Agent(s) used [reference]	Evaluable patients	Progressive disease as best response	Complete remission	Major toxicity (in treatment groups)	
				All grade (%)	Grade 3/4 (%)
Sorafenib [Escudier *et al.* 2007b]	451	29 (9%)	1 (<1%)*	Diarrhea (48), rash/ desquamation (41), hand–foot syndrome (33)	Hand–foot syndrome (6), HTN (6), cardiac ischemia/infarction (3)
Sunitinib [Motzer *et al.* 2009b]	374	26 (7%)	11 (2.9%)*	Anemia (79), lymphopenia (78), neutropenia (77), diarrhea (61), fatigue (54)	Neutropenia (18), lymphopenia (18), HTN (12), fatigue (11)
Bevacizumab + IFN-α [Escudier *et al.* 2007b]	306	61 (20%)	2 (<1%)*	Pyrexia (45), anorexia (36), bleeding (33), fatigue (33)	Fatigue (12), asthenia (10)
Bevacizumab + IFN-α [Rini *et al.* 2008]	350	NR	2 (<1%)*	Fatigue (93), proteinuria (71), anorexia (58), neutropenia (43)	Fatigue (37), anorexia (17), proteinuria (15)
Pazopanib [Sternberg *et al.* 2010]	290	51 (18%)	1 (<1%)	Diarrhea (52), ↑ ALT/AST (53), HTN (40)	↑ALT (12), ↑AST (8), hyponatremia (5)
Temsirolimus [Hudes *et al.* 2007]	210	NR	NR	Asthenia (51), rash (47), anemia (45)	Anemia (20), asthenia (11), hyperglycemia (11)
Everolimus [Motzer *et al.* 2008]	272	53 (19%)	NR	Anemia (91), hypercholesterolemia (76), hypertriglyceridemia (71), stomatitis (40)	Lymphopenia (15), anemia (9)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HTN, hypertension; IFN, interferon; NR, not reported.
*Investigator assessment.

as yet undefined), and the benefit is primarily control of disease burden, with the majority of patients who benefit achieving stable disease. The role of consolidative surgery in patients with a major response to targeted therapy (i.e. a surgical CR) is not yet well defined.

A significant proportion of patients are primary refractory to targeted therapy and the mechanisms of resistance are unknown

A significant number of patients treated with targeted therapy are primarily refractory to treatment, with progressive disease as a best response (Table 2). In the treatment arm of the sorafenib trial, 9% of patients had progressive disease as best response [Escudier *et al.* 2007a], and 7% progressed initially on sunitinib. In the AVOREN trial, 20% of patients progressed on treatment with bevacizumab and IFN-α [Escudier *et al.* 2007b], and 19% of patients progressed on treatment with everolimus [Hudes *et al.* 2007], as did 37% of patients treated with everolimus [Motzer *et al.* 2010]. There were 18% of patients who had progressive disease as best response while being treated with pazopanib [Sternberg *et al.* 2010]. A recent systematic review collected data on patients with mRCC treated with anti-VEGF therapy across 12 centers [Heng *et al.* 2011]. Of 1056 patients initially treated with sorafenib, sunitinib or bevacizumab, 26% were primarily refractory to treatment, with PD as best response [Heng *et al.* 2011]. A total of 40% of VEGF-refractory patients received further systemic therapies, with a uniform dismal outcome regardless of type of subsequent therapy received [Heng *et al.* 2011]. While mRCC patients who are primary refractory to anti-VEGF therapies have a dismal prognosis, it is unclear what the next best step is, and second-line anti-mTOR and anti-VEGF agents produce similar poor outcomes. Enrollment on a clinical trial is thus preferred for these patients. Preclinical evidence suggests that resistance may be mediated by non-VEGF factors, although the exact mechanisms have not been elucidated [Rini and Atkins, 2009].

The majority of agents have been unable to demonstrate an overall survival benefit

With the exception of temsirolimus, the OS data in all the aforementioned studies have had *p* values >0.05. While this is felt to be due to crossover in large part, as patients in several studies were allowed to cross over to the treatment arm after progressing on placebo, the significant PFS advantages of targeted therapy over inactive therapy have not readily translated into demonstrable OS benefits. While this has not yet impacted the ability of drugs to receive FDA approval, as more data emerges on survival, the FDA may become more hesitant to approve drugs with considerable toxicity without a proven OS benefit. It is clear, however, that the population of metastatic RCC patients treated in the era of targeted therapy is living longer than patients from the cytokine era. This is also evidenced by the very long survival of patients initially randomized to cytokines on the phase III trials, whose survival no doubt is prolonged by the receipt of subsequent active therapy.

Inclusion of different histologic subtypes in clinical trials

The Heidelberg classification includes four subtypes of RCC: clear cell adenocarcinoma (75%), papillary (12%), chromophobe (4%), oncocytoma (4%), unclassified (4%, including sarcomatoid features) and collecting duct (<1%) RCC [Cohen and McGovern, 2005]. However, of the aforementioned trials, with the exception of the Global ARCC temsirolimus trial, all trials included patients with clear cell or predominantly clear cell histology (in the temsirolimus trial, 80% were clear cell and 20% were classified as 'other') [Hudes *et al.* 2007]. There is therefore a paucity of data on how other histologic subtypes respond to targeted therapy, and whether toxicities in this population are different than those experienced by the clear cell RCC population. Moreover, the vast majority of patients in trials have clear cell RCC, and this model does not take into consideration 25% of the at large RCC population. While some patients with a good risk profile and clear cell histology mRCC have drawn clinical benefit from IL-2 or IFN-α immunotherapy [Ljungberg *et al.* 2007], objective response rates of less than 5% have been reported with immunotherapy of nonclear-cell RCC subtypes [Motzer *et al.* 2002; Upton *et al.* 2005], suggesting different molecular pathophysiology. While the initial trials generally excluded nonclear-cell histology, there is some data on the efficacy of targeted therapy in various mRCC subtypes. In the worldwide sunitinib expanded-access program (EAP), 11.8% of patients had nonclear cell histology, and 5.4% of these patients had a response rate, compared with 9.3% of the overall population [Gore *et al.* 2009]. An expanded-access sorafenib trial assessed the efficacy of sorafenib in an advanced nonclear-cell RCC population, of which 8.5% had chromophobe, papillary, collecting duct or oncocytoma histology. Of the patients with papillary and chromophobe RCC who were evaluable, 3.4% *versus* 5.5%, respectively, had partial response, and 7 7.1% *versus* 88.8%, respectively, had stable disease [Stadler *et al.* 2010]. In addition, a recent analysis of temsirolimus *versus* IFN-α in patients with untreated advanced RCC demonstrated that temsirolimus is active in both clear-cell and other histological subtypes: patients with clear-cell and other RCC histologies, mostly papillary, had comparable median OS and PFS [Dutcher *et al.* 2009]. Nonetheless, there is limited data in nonclear cell RCC and the treatment of choice for such patients is a clinical trial pending a deeper understanding of the underlying biology of these alternative histologies.

The safety and efficacy of targeted therapy on brain metastases is unclear

Occult brain metastases at the time of diagnosis of mRCC are not uncommon, with an incidence ranging from 2% to 17% [Sheehan *et al.* 2003; Shuch *et al.* 2008]. The consensus appears to be that patients with mRCC may benefit from initial screening in order to identify smaller lesions that are amenable to less invasive treatment, such as stereotactic radiosurgery, as this may increase survival in a select group of patients [Sheehan *et al.* 2003; Shuch *et al.* 2008]. However, patients with RCC brain metastasis (RCCBM) often do not fulfill inclusion criteria of clinical trials. Patients included in clinical trials are not necessarily representative of the general population, and patients with RCCBM have limited treatment options [Remon *et al.* 2011]. The sunitinib EAP revealed that 7% of patients in the trial had brain metastases. Median PFS was 5.6 months in the brain metastases group and 10.9 months for the overall population, while median OS was 9.2 months for patients with brain metastases and 18.4 months for the overall population [Gore *et al.* 2009]. Assessment of response was not included in the treatment

protocol, and it is therefore challenging to infer whether or not treatment with sunitinib is equally effective in mRCC patients and patients with RCCBM. Interestingly, the safety profile of sunitinib was comparable in patients with or without brain metastases [Gore *et al.* 2009]. In sorafenib's EAP, 3.7% of evaluable patients had brain metastases. This study reported survival data for the overall population, and did not report data on patients with brain metastases [Stadler *et al.* 2010], making it challenging to conclude whether or not sorafenib is effective in this population. Anti-VEGF therapies disrupt tumor vasculature, and therefore may potentially increase the incidence of bleeding in patients with RCCBM [Kamba and McDonald, 2007]. Furthermore, RCCBM patients may be at increased risk of spontaneous intracranial bleeding [Bitoh *et al.* 1984; Remon *et al.* 2011]. Both phase III trials assessing bevacizumab excluded patients with RCCBM, and neither of these reported the incidence of central nervous system (CNS) bleeding. Given the paucity of data from the primary trials on the risk of intracranial hemorrhage in patients with RCCBM, a systematic review including a total of 57 trials addressed this issue [Carden *et al.* 2008]. A total of 16 of these trials (12 phase I/II and 4 randomized, phase III trials) included patients with brain metastases. Interestingly, only one episode of intracranial bleeding was recorded from the phase I/II trials, and none with the phase III [Carden *et al.* 2008], suggesting anti-VEGF inhibitors are safe in the treatment of patients with RCCBM. A study that aimed to evaluate the impact of TKIs on the incidence of brain metastasis and OS in patients with mRCC revealed that OS was significantly longer in the TKI treated group (25 months *versus* 12.1 months, $p < 0.001$) [Verma *et al.* 2011]. Furthermore, the 5-year actuarial rate of brain metastasis was 40% in the non-TKI treated group *versus* 17% in the TKI treated group ($p < 0.001$), and treatment with TKIs was associated with a significantly lower incidence of brain metastasis ($p < 0.003$) [Verma *et al.* 2011], suggesting that TKIs may play a role in the prevention of RCCBM in patients with mRCC. At present, appropriate local therapy (i.e. surgery, radiation) should be undertaken prior to initiation of targeted therapy, which appears safe in this setting. Efficacy against CNS metastases and use of alternative therapies in this setting requires further investigation.

Chronic, ongoing therapy is associated with ongoing toxicity

The clinical benefits offered by targeted therapies allow for a prolonged duration of treatment, and safety data accumulated from multiple trials has allowed for the description of toxicity profiles of these novel agents. The crucial clinical trials of targeted therapy for RCC included a total of 4511 patients [Ravaud, 2011]. In all but the AVOREN trial, treatment continued until PD or unacceptable toxicity. While toxicity is common, most AEs are grade 1 or 2 in severity, and are managed by supportive treatment and dose reduction or treatment interruption.

Bevacizumab. In the AVOREN trial, among the most common all-grade and grade 3 or 4 adverse events (AEs) were fatigue and asthenia across all groups [Escudier *et al.* 2007b; Rini *et al.* 2010]. Adding Bevacizumab to IFN-α led to increased incidence of hypertension, bleeding and proteinuria [Escudier *et al.* 2007b], while gastrointestinal perforation, arterial thromboembolic events (ATEs), complications of wound healing and congestive heart failure, all known complications of bevacizumab, occurred at grade 3 or 4 toxicity at an incidence of ≤1% [Escudier *et al.* 2007b]. In CALGB 90206, the double treatment arm most commonly experienced fatigue, nausea, hypertension, proteinuria, neutropenia and nausea, and grade 3 toxicity was significantly greater when bevacizumab given with IFN-α, compared with IFN-α alone [Rini *et al.* 2010]. There are dose reduction recommendations for IFN-α, but none for bevacizumab, and patients with AEs are instead managed with treatment interruption or cessation [Ravaud, 2011].

Sunitinib. The most common grade 3 or 4 AEs were hypertension (8%), fatigue (7%), diarrhea and hand–foot syndrome (both 5%), and the incidence of all but fatigue were significantly higher with sunitinib that IFN ($p < 0.05$) [Motzer *et al.* 2009b]. A recent meta-analysis of incidence of arterial thromboembolic events (ATEs) in patients receiving sorafenib or sunitinib indicates that sunitinib's ATE incidence is 1.3% in patients with RCC (95% CI 1.0–1.6%) [Choueiri *et al.* 2010; Ravaud, 2011]. Decline of left ventricular ejection fraction (LVEF) occurred in 13% of sunitinib patients (compared with 3% of IFN patients) [Motzer *et al.* 2009b], and hypothyroidism was reported in 14% of patients receiving sunitinib (*versus* 3% on IFN) [Motzer *et al.*

2009b]. As these agents become more widely used, monitoring patient's blood pressure (BP) throughout treatment, using antihypertensive agents as adjunctive treatment, measuring baseline LVEF, and routine thyroid function screening in patients experiencing fatigue would allow for the development of standard practice guidelines and may allow longer treatment [Ravaud, 2011]

Sorafenib. In the TARGET trial, the most common grade 3 and 4 AEs were hand–foot syndrome (6% *versus* 0.4% with placebo), cardiac ischemia/infarction (3% *versus* 0.4% with placebo) and hypertension (6% *versus* 0% with placebo) [Escudier *et al.* 2007a, 2009]. Similar to sunitinib, routine monitoring of BP may allow for prolonged treatment. In the previously mentioned meta-analysis of ATEs with sorafenib and sunitinib, the ATE incidence was 1.7% (95% CI 1.1–2.4%) [Choueiri *et al.* 2010]. Taken together, the relative risk (RR) for an ATE with sorafenib or sunitinib is significantly increased at 3.0 (95% CI 1.3–7.4, $p = 0.015$) [Choueiri *et al.* 2010; Ravaud, 2011].

Pazopanib. The most common all-grade toxicities with pazopanib were diarrhea (52% *versus* 9% with placebo) increases in aspartate aminotransferase/alanine aminotransferase (AST/ALT) (53% *versus* 2% with placebo) and hypertension (40% *versus* 10% with placebo). Diarrhea and hypertension occurred at an incidence of ≤3% as grade 3 or 4 toxicities [Sternberg *et al.* 2010], whereas increases in ALT and AST accounted for 12% and 8% of grade 3/4 toxicities, respectively [Sternberg *et al.* 2010]. Hemorrhage occurred at a rate of 13% in the pazopanib arm (*versus* 5% of placebo), and there have been reports of fatal hepatotoxicity and severe proteinuria, leading to recommendations for routine testing of liver function and urinalysis [Ravaud, 2011].

Temsirolimus. The most common AE in all groups was asthenia (51% with temsirolimus monotherapy *versus* 64% with interferon monotherapy), followed by rash (47% with temsirolimus monotherapy *versus* 6% with interferon monotherapy) [Hudes *et al.* 2007]. The most common grade 3 or 4 AE with temsirolimus monotherapy was anemia (20%), and hyperglycemia occurred at an incidence of 11% [Hudes *et al.* 2007].

Everolimus. Grade 1 or 2 stomatitis and infections were the most common adverse events, occurring in 40% and 10% of patients treated with everolimus, respectively [Motzer *et al.* 2008], and anemia was the most common laboratory abnormality, occurring in 91% of patients [Motzer *et al.* 2008]. Lymphopenia (15%), anemia (9%), and infections (2%) were the most common grade 3 or 4 toxicities [Motzer *et al.* 2008]. Pneumonitis was reported in 30 patients receiving everolimus [Motzer *et al.* 2008]. Patient education and frequent screening may lead to patients presenting at earlier grades of toxicity. While novel therapies are associated with multiple toxicities that are less commonly seen with more common chemotherapy and immunotherapy, these toxicities can affect patient QOL and require intensive monitoring and nursing support for optimal management.

RECIST, which considers only size changes, is often inaccurate in determining progression

RECIST criteria were initially developed in 2000, and are used by clinical trials to assess for response to treatment using the sum of the greatest diameter of the tumors [Therasse *et al.* 2000]. Several studies have assessed reproducibility of tumor measurements, and within-subject coefficient variation (wCV) ranges from 14% to 34% [Laking *et al.* 2006; Mazumdar *et al.* 2004]. Not surprisingly, interobserver variability is significantly higher for irregular lesions than for smaller ones [Marcus *et al.* 2009], and for difficult to delineate lesions, such as hepatic and pelvic masses [Hopper *et al.* 1996]. Targeted therapies interfere with aberrant pathways of tumorigenesis, including angiogenesis and neovascularization. The gold standard for assessing angiogenesis (histology) is invasive. Several agents have been shown to cause necrosis and cystic changes in solid tumors, and this does not always correlate with tumor shrinkage [Nishino *et al.* 2010; Shankar *et al.* 2009], and thus the effect of target therapy may be underestimated using RECIST. For example, neither sorafenib nor bevacizumab achieved significant ORRs using RECIST criteria, but both led to overall tumor burden reduction in the majority of patients and significantly increased PFS, suggesting clinical efficacy [Motzer *et al.* 2009a; Rini *et al.* 2010]. Functional imaging modalities such as dynamic contrast enhanced imaging with computed tomography (CT) or magnetic resonance imaging (MRI) may quantify changes of vascularity, permeability and the degree of necrosis as an indication of overall disease response criteria [Chalian *et al.* 2011; Drevs *et al.* 2002; Marcus

et al. 2009]. Nonetheless, CT is likely to be the modality of choice as functional imaging is not yet routine. Physicians need to account for overall patient clinical status, necrosis of lesions despite size increase, and small size increases which may be a 20% increase from nadir but represent only minimal change and not true progression. Routine review of actual images and not only radiology reports is mandatory to continue therapy appropriately.

Dosing

The current recommended dose for sunitinib is 50 mg once daily, 4 weeks on followed by 2 weeks off. Importantly, a study found that the steady-state area under the curve (AUC) of total drug (sunitinib and its primary active metabolite, SU12662), were significantly associated with longer time to tumor progression (TTP) and OS in patients with mRCC [Houk *et al.* 2010]. In addition, steady-state AUC of sunitinib correlated with significantly increased objective response and response probability in patients with mRCC, and also correlated with stable disease in patients with mRCC [Houk *et al.* 2010]. Furthermore, there was a significant correlation between dose and tumor size reductions [Houk *et al.* 2010]. This data emphasizes the importance of maintaining patients on an adequate dose of sunitinib, in addition to avoiding dosing interruptions or dose titrations that may affect the steady-state AUC during treatment. While data shows that higher drug levels lead to better outcomes, we cannot currently measure drug levels in the clinic, and are forced to dose empirically, starting everyone at a given dose and adjusting based on toxicity. Real-time drug level monitoring may allow for more effective treatment, with better outcomes, in the mRCC population. Further studies to individually optimize dose for all targeted therapies are needed.

Lack of predictive biomarkers

Predictive molecular markers for RCC have generated great interest, but none of these has been found to reliably predict outcomes in patients with RCC. It is beyond the scope of this article to fully review the evidence for the prognostic importance of molecular markers. Hypertension is a common side effect in patients treated with angiogenesis inhibitors that target the VEGF pathway, including sunitinib, sorafenib and bevacizumab [Humphreys and Atkins, 2009; Launay-Vacher and Deray, 2009; Roodhart *et al.* 2008]. It was shown that mRCC patients with sunitinib-induced hypertension had better outcomes than those who did not develop treatment-induced systolic hypertension (ORR 54.8% *versus* 8.7%, $p < 0.001$ and OS 30.9 months *versus* 7.2 months, $p < 0.001$) [Rini *et al.* 2011a]. These results were comparable when diastolic hypertension was assessed [Rini *et al.* 2011a]. Few cardiovascular, cerebrovascular, ocular or renal adverse events were observed, and these were comparable between patients with and without hypertension [Rini *et al.* 2011a]. Another study found that patients treated with axitinib (a VEGFR inhibitor) who developed diastolic blood pressure (DBP) >90 mmHg had a significantly lower relative risk of death than patients with DBP <90 mmHg ($p < 0.001$) [Rini *et al.* 2011b]. Furthermore, the relative risk of progression was also lower in patients with DBP >90 mmHg, although this did not reach statistical significance [Rini *et al.* 2011b]. ORR was significantly higher ($p < 0.001$) in the group that developed diastolic hypertension [Rini *et al.* 2011b]. Median OS and PFS were higher for patients with DBP >90 mmHg, and again, AEs were comparable, regardless of whether or not patients developed hypertension [Rini *et al.* 2011b]. These studies indicate that blood pressure measurements may identify which patients will have better responses to therapy, although the clinical application of these data awaits further study. A study that assessed whether single nucleotide polymorphisms (SNPs) were associated with response in the treatment of advanced RCC with sunitinib [Garcia-Donas *et al.* 2011]; of 16 polymorphisms in nine genes, two VEGFR3 missense polymorphisms were associated with reduced PFS, and a high metabolizing cytochrome CYP3A5*1 allele was associated with increased risk of toxicity causing dosing reductions [Garcia-Donas *et al.* 2011]. Another study found that mRCC patients with genetic polymorphisms in three genes implicated in sunitinib metabolism had prolonged PFS when treated with sunitinib [van der Veldt *et al.* 2011], suggesting that gene analysis may allow for prognostication of treatment efficacy. These preliminary data generate hypotheses about genetic variations that may allow for prediction of treatment benefit. Truly personalized therapy based on a biomarker in RCC, however, awaits further study.

Conclusion

Elucidation of the molecular mechanisms of RCC has allowed for the development, and subsequent approval of multiple targeted agents for the treatment of advanced RCC. There are clear effects as evidenced by significant objective response rates, longer disease control, and mRCC patients are living longer. Nonetheless, significant challenges still face this field. Few patients achieve CRs, and a considerable number are primary refractory to these agents, with all patients eventually developing resistance. At present, treatments are providing palliation and increasing PFS, but require ongoing therapy. There is a significant learning curve to the proper administration of these agents considering toxicity management, maintenance of dosing and interpretation of radiographs. Efforts to develop predictive biomarkers are at the forefront of research to overcome some of the challenges and further advance the care of RCC patients.

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References

Bitoh, S., Hasegawa, H., Ohtsuki, H., Obashi, J., Fujiwara, M. and Sakurai, M. (1984) Cerebral neoplasms initially presenting with massive intracerebral hemorrhage. *Surg Neurol* 22: 57–62.

Carden, C.P., Larkin, J.M. and Rosenthal, M.A. (2008) What is the risk of intracranial bleeding during anti-VEGF therapy? *Neuro Oncol* 10: 624–630.

Chalian, H., Tore, H.G., Horowitz, J.M., Salem, R., Miller, F.H. and Yaghmai, V. (2011) Radiologic assessment of response to therapy: comparison of RECIST versions 1.1 and 1.0. *Radiographics* 31: 2093–2105.

Choueiri, T.K., Schutz, F.A., Je, Y., Rosenberg, J.E. and Bellmunt, J. (2010) Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol* 28: 2280–2285.

Cohen, H.T. and McGovern, F.J. (2005) Renal-cell carcinoma. *N Engl J Med* 353: 2477–2490.

Drevs, J., Muller-Driver, R., Wittig, C., Fuxius, S., Esser, N., Hugenschmidt, H. *et al.* (2002) PTK787/ZK 222584, a specific vascular endothelial growth factor-receptor tyrosine kinase inhibitor, affects the anatomy of the tumor vascular bed and the functional vascular properties as detected by dynamic enhanced magnetic resonance imaging. *Cancer Res* 62: 4015–4022.

Dutcher, J.P., de Souza, P., McDermott, D., Figlin, R.A., Berkenblit, A., Thiele, A. *et al.* (2009) Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol* 26: 202–209.

Escudier, B., Bellmunt, J., Negrier, S., Bajetta, E., Melichar, B., Bracarda, S. *et al.* (2010) 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* 28: 2144–2150.

Escudier, B., Chevreau, C., Lasset, C., Douillard, J.Y., Ravaud, A., Fabbro, M. *et al.* (1999) Cytokines in metastatic renal cell carcinoma: is it useful to switch to interleukin-2 or interferon after failure of a first treatment? Groupe Francais d'Immunotherape. *J Clin Oncol* 17: 2039–2043.

Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Siebels, M. *et al.* (2007a) Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356: 125–134.

Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Staehler, M. *et al.* (2009) Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 27: 3312–3318.

Escudier, B., Pluzanska, A., Koralewski, P., Ravaud, A., Bracarda, S., Szczylik, C. *et al.* (2007b) Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 370: 2103–2111.

Garcia-Donas, J., Esteban, E., Leandro-Garcia, L.J., Castellano, D.E., del Alba, A.G., Climent, M.A. *et al.* (2011) Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. *Lancet Oncol* 12: 1143–1150.

Gore, M.E., Szczylik, C., Porta, C., Bracarda, S., Bjarnason, G.A., Oudard, S. *et al.* (2009) Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* 10: 757–763.

Heng, D.Y., Mackenzie, M.J., Vaishampayan, U.N., Bjarnason, G.A., Knox, J.J., Tan, M.H. *et al.* (2011) Primary anti-vascular endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma:

clinical characteristics, risk factors, and subsequent therapy. *Ann Oncol*, in press.

Hopper, K.D., Kasales, C.J., Van Slyke, M.A., Schwartz, T.A., TenHave, T.R. and Jozefiak, J.A. (1996) Analysis of interobserver and intraobserver variability in CT tumor measurements. *AJR Am J Roentgenol* 167: 851–854.

Houk, B.E., Bello, C.L., Poland, B., Rosen, L.S., Demetri, G.D. and Motzer, R.J. (2010) Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol* 66: 357–371.

Hudes, G., Carducci, M., Tomczak, P., Dutcher, J., Figlin, R., Kapoor, A. *et al.* (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 356: 2271–2281.

Humphreys, B.D. and Atkins, M.B. (2009) Rapid development of hypertension by sorafenib: toxicity or target? *Clin Cancer Res* 15: 5947–5949.

Hutson, T.E. (2011) Targeted therapies for the treatment of metastatic renal cell carcinoma: clinical evidence. *Oncologist* 16(Suppl. 2): 14–22.

Janzen, N.K., Kim, H.L., Figlin, R.A. and Belldegrun, A.S. (2003) Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. *Urol Clin North Am* 30: 843–852.

Jemal, A., Siegel, R., Xu, J. and Ward, E. (2010) Cancer statistics, 2010. *CA Cancer J Clin* 60: 277–300.

Kamba, T. and McDonald, D.M. (2007) Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer* 96: 1788–1795.

Laking, G.R., West, C., Buckley, D.L., Matthews, J. and Price, P.M. (2006) Imaging vascular physiology to monitor cancer treatment. *Crit Rev Oncol Hematol* 58: 95–113.

Launay-Vacher, V. and Deray, G. (2009) Hypertension and proteinuria: a class-effect of antiangiogenic therapies. *Anticancer Drugs* 20: 81–82.

Ljungberg, B., Hanbury, D.C., Kuczyk, M.A., Merseburger, A.S., Mulders, P.F., Patard, J.J. *et al.* (2007) Renal cell carcinoma guideline. *Eur Urol* 51: 1502–1510.

Marcus, C.D., Ladam-Marcus, V., Cucu, C., Bouche, O., Lucas, L. and Hoeffel, C. (2009) Imaging techniques to evaluate the response to treatment in oncology: current standards and perspectives. *Crit Rev Oncol Hematol* 72: 217–238.

Mazumdar, M., Smith, A. and Schwartz, L.H. (2004) A statistical simulation study finds discordance between WHO criteria and RECIST guideline. *J Clin Epidemiol* 57: 358–365.

Motzer, R.J., Bacik, J., Mariani, T., Russo, P., Mazumdar, M. and Reuter, V. (2002) Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. *J Clin Oncol* 20: 2376–2381.

Motzer, R.J., Escudier, B., Oudard, S., Hutson, T.E., Porta, C., Bracarda, S. *et al.* (2010) Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer* 116: 4256–4265.

Motzer, R.J., Escudier, B., Oudard, S., Hutson, T.E., Porta, C., Bracarda, S. *et al.* (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 372: 449–456.

Motzer, R.J., Hudes, G., Wilding, G., Schwartz, L.H., Hariharan, S., Kempin, S. *et al.* (2009a) Phase I trial of sunitinib malate plus interferon-alpha for patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer* 7: 28–33.

Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Oudard, S. *et al.* (2009b) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 27: 3584–3590.

Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Rixe, O. *et al.* (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 356: 115–124.

Nishino, M., Jagannathan, J.P., Ramaiya, N.H. and Van den Abbeele, A.D. (2010) Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol* 195: 281–289.

Oudard, S., George, D., Medioni, J. and Motzer, R. (2007) Treatment options in renal cell carcinoma: past, present and future. *Ann Oncol* 18(Suppl. 10): x25–x31.

Ravaud, A. (2011) Treatment-associated adverse event management in the advanced renal cell carcinoma patient treated with targeted therapies. *Oncologist* 16(Suppl. 2): 32–44.

Remon, J., Lianes, P. and Martinez, S. (2011) Brain metastases from renal cell carcinoma. Should we change the current standard? *Cancer Treat Rev*, in press.

Rini, B.I. and Atkins, M.B. (2009) Resistance to targeted therapy in renal-cell carcinoma. *Lancet Oncol* 10: 992–1000.

Rini, B.I., Cohen, D.P., Lu, D.R., Chen, I., Hariharan, S., Gore, M.E. *et al.* (2011a) Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 103: 763–773.

Rini, B.I., Halabi, S., Rosenberg, J.E., Stadler, W.M., Vaena, D.A., Archer, L. *et al.* (2010) 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* 28: 2137–2143.

Rini, B.I., Halabi, S., Rosenberg, J.E., Stadler, W.M., Vaena, D.A., Ou, S.S. *et al.* (2008) Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* 26: 5422–5428.

Rini, B.I., Schiller, J.H., Fruehauf, J.P., Cohen, E.E., Tarazi, J.C., Rosbrook, B. *et al.* (2011b) Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. *Clin Cancer Res* 17: 3841–3849.

Roodhart, J.M., Langenberg, M.H., Witteveen, E. and Voest, E.E. (2008) The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway. *Curr Clin Pharmacol* 3: 132–143.

Shankar, L.K., Van den Abbeele, A., Yap, J., Benjamin, R., Scheutze, S. and Fitzgerald, T.J. (2009) Considerations for the use of imaging tools for phase II treatment trials in oncology. *Clin Cancer Res* 15: 1891–1897.

Sheehan, J.P., Sun, M.H., Kondziolka, D., Flickinger, J. and Lunsford, L.D. (2003) Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. *J Neurosurg* 98: 342–349.

Shuch, B., La Rochelle, J.C., Klatte, T., Riggs, S.B., Liu, W., Kabbinavar, F.F. *et al.* (2008) Brain metastasis from renal cell carcinoma: presentation, recurrence, and survival. *Cancer* 113: 1641–1648.

Stadler, W.M., Figlin, R.A., McDermott, D.F., Dutcher, J.P., Knox, J.J., Miller, W.H., Jr. *et al.* (2010) Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer* 116: 1272–1280.

Sternberg, C.N., Davis, I.D., Mardiak, J., Szczylik, C., Lee, E., Wagstaff, J. *et al.* (2010) Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 28: 1061–1068.

Therasse, P., Arbuck, S.G., Eisenhauer, E.A., Wanders, J., Kaplan, R.S., Rubinstein, L. *et al.* (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92: 205–216.

Upton, M.P., Parker, R.A., Youmans, A., McDermott, D.F. and Atkins, M.B. (2005) Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy. *J Immunother* 28: 488–495.

van der Veldt, A.A., Eechoute, K., Gelderblom, H., Gietema, J., Guchelaar, H.J., van Erp, N.P. *et al.* (2011) Genetic polymorphisms associated with a prolonged progression-free survival in patients with metastatic renal cell cancer treated with sunitinib. *Clin Cancer Res* 17: 620–629.

Verma, J., Jonasch, E., Allen, P., Tannir, N. and Mahajan, A. (2011) Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. *Cancer* 117: 4958–4965.