Targeted therapy in renal cancer

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Abstract: Renal cell cancer (RCC) has an increasing incidence internationally and is a disease for which there have been limited therapeutic options until recently. The last decade has seen a vastly improved understanding of the biological and clinical factors that predict the outcome of this disease. We now understand some of the different molecular underpinnings of renal clear cell carcinoma by mutation or silencing of the von Hippel Lindau (VHL) gene and subsequent deregulated proliferation and angiogenesis. Survival in advanced disease is predicted by factors (performance status, anemia, hypercalcemia, and serum lactate dehydrogenase, time from diagnosis to recurrence) incorporated into the Memorial Sloan Kettering Cancer Center (MSKCC) criteria (also referred to as 'Motzer' criteria). These criteria allow classification of patients with RCC into good, intermediate and poor risk categories with median overall survivals of 22 months, 12 months and 5.4 months, respectively. Predicated upon these advances, six new targeted drugs (sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab and pazopanib) have been tested in well-designed phase III trials, selected or stratified for MSKCC risk criteria, with positive results. All of these new drugs act at least in part through vascular endothelial growth factor (VEGF) mediated pathways with other potential therapeutic impact on platelet-derived growth factor (PDGF), raf kinase and mammalian target of rapamycin (mTOR) pathways. Importantly, data from each of these trials show a consistent doubling of progression-free survival (PFS) over prior standard of care treatments. In addition, sorafenib, sunitinib and temsirolimus, have demonstrated significant overall survival (OS) benefits as well; further follow-up is required to determine whether the disease control exhibited by everolimus and pazopanib will translate into a survival advantage. These drugs are generally well tolerated, as demonstrated by quality-of-life improvement in clinical trials, and result in clinical benefit for in excess of 70% of patients treated. They have challenged the traditional outcomes of clinical trial design by achieving their benefits with relatively few radiographic responses, but high rates of disease stability. The unique side-effect profile coupled with the chronicity of therapy requires increased vigilance to maximize exposure to the drugs while maintaining quality of life and minimizing toxicity. This review focuses on the background, clinical development and practical use of these new drugs in RCC.

Keywords: renal cell carcinoma, bevacizumab, everolimus, sorafenib, sunitinib, temsirolimus

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Introduction

The incidence of renal cell cancer (RCC) is rising [Decastro and Mckiernan, 2008; Mathew *et al.* 2002; Chow *et al.* 1999]. The precise reason for this is unclear but may relate to the higher prevalence of risk factors such as obesity, hypertension and tobacco abuse and the broader use of imaging technology in many populations. While still an uncommon disease, RCC presents a unique paradigm for cancer therapeutics because of relatively limited genetic heterogeneity compared to other cancers. This relative homogeneity has allowed the delineation of different pathological subgroups of RCC: clear *versus* non-clear cell. In addition, it has meant molecular characterization of tumors that will eventually allow integration of tumor genetics into clinical nomograms that predict response to specific agents and ideally survival. Detailed understanding of the RCC clinical-pathological-molecular phenotype has already guided therapeutic development, and has the potential to foster individualized therapy algorithms. From a practical cancer therapy standpoint, six novel targeted agents in the last 3 years have been found to double progression-free survival (PFS), with three of these

drugs demonstrating significant overall survival (OS) benefit. In doing so RCC has served as a vehicle for five new oncology drugs. Although these successes may have begun the transformation of RCC into a chronic condition, cure for patients with advanced RCC is rare, and remains the goal of ongoing investigations.

The clinical molecular biology of renal cell cancer

From a molecular perspective, cancer is characterized by a number of hallmark molecular changes [Hanahan and Weinberg, 2000]. In common with many other malignancies, RCC has an anomalous or aberrant function on a number of key cellular pathways and paracrine/autocrine regulatory loops, including: attenuated immune surveillance, angiogenesis, signal transduction, cell-cycle regulation, apoptosis, extracellular matrix modulation, and regulation of transcription. Factors and clinical implications for these alterations are summarized in Table 1. Of all these, clear cell RCC is uniquely dependent upon two factors: dyskinetic angiogenesis and immune dysfunction.

The angiogenic phenotype is crucial in both tumor progression and metastasis [Fidler and Ellis, 1994]. The key factor involved in signaling for angiogenesis in nearly all human tumors is vascular endothelial growth factor (VEGF) [Dvorak *et al.* 1995; Senger *et al.* 1993] (Figure 1). VEGF and its receptors are critical for healthy blood vessel formation [Carmeliet *et al.* 1996; Ferrara *et al.* 1996; Fong *et al.* 1995; Shalaby *et al.* 1995]; increased expression of VEGF receptors on endothelial cells within the tumor vasculature suggests it is also important in tumor angiogenesis [Chan *et al.* 1998; Leung *et al.* 1997; Cheng *et al.* 1996]. VEGF is crucial for the development of tumor masses exceeding a diameter of 3–5 mm [Kim *et al.* 1993].

As noted above, increased expression of VEGF and its receptors is common and prognostic in RCC [Slaton *et al.* 2001; Dosquet *et al.* 1997; Takahashi *et al.* 1994; Brown *et al.* 1993]; the mechanism of VEGF dysregulation is linked to the Von-Hippel Lindau (VHL) gene. There is a high frequency of VHL gene abnormalities in both familial and sporadic cases of RCC [Maher and Kaelin, 1997; Prowse *et al.* 1997; Gnarra *et al.* 1996a]. In sporadic RCC of clear cell type, mutations of VHL are found in 75% of the tumors [Na *et al.* 2003; Vogelzang and Stadler, 1998]. Another 10–25% of patients have hypermethylation of the VHL promoter region, which leads to suppressed mRNA and protein production, and loss of VHL activity. VHL protein (VHLp) acts as a component of ubiquitin E3 ligase and those VHL mutations commonly seen in RCC result in loss of this ligase activity [Hansen *et al.* 2002; Hon *et al.* 2002; Clifford *et al.* 2001; Iwai *et al.* 1999; Duan *et al.* 1995]. When tissue oxygen levels are normal, this ligase activity and other actions of wild-type VHLp down-regulate VEGF expression through proteolytic, post-translational control of hypoxia-inducible factors (HIFs) 1 and 2 [Clifford and maher, 2001; Gunningham *et al.* 2001; Krieg *et al.* 2000; Gnarra *et al.* 1996b; Iliopoulos *et al.* 1996]. In conditions of hypoxia or VHLp dysfunction, HIFs accumulate to concentrations that increase the expression of various molecular growth factors, including VEGF and platelet-derived growth factor (PDGF) [Mack *et al.* 2003; Maxwell *et al.* 1999; Thrash-Bingham and Tartof, 1999; Iliopoulos *et al.* 1996]. These growth factors bind to specific tyrosine kinase receptors (TKRs) on the surface of endothelial cells and vascular pericytes respectively, resulting in cell migration, proliferation, survival, and tumor angiogenesis [Wykoff *et al.* 2004]. HIFs may, under certain conditions, also regulate epidermal growth factor (EGF), which along with VEGF stimulates proliferation of epithelial renal cancer cells [Gunaratnam *et al.* 2003]. To summarize, the vast majority of patients with clear cell RCC have tumors in which VHL is not functional, leading to increased angiogenesis.

Tumor angiogenesis is also stimulated through the PI3K (phosphatidylinositol-3 kinase) – AKT – mammalian target of rapamycin (mTOR) pathway and agents inhibiting the activity of this pathway may be expected to have activity in RCC and other cancers [Del Bufalo *et al.* 2006; Majumder *et al.* 2004; Brugarolas *et al.* 2003; Kenerson *et al.* 2002]. mTOR regulates a number of molecular and cellular functions including proliferation through c-myc and cyclin dependent kinases and angiogenesis through the regulation of HIF [Del Bufalo *et al.* 2006; Kenerson *et al.* 2002; Blancher *et al.* 2001]. This pathway is up-regulated in a significant proportion of patients with poor-risk RCC according to Memorial Sloan Kettering Cancer Center (MSKCC) criteria, making its components attractive targets in this group of

Table 1. Summary of molecular aberrancy in renal cell cancer (RCC).

	Specific factor	Effect	Outcome or clinical correlated	References
Angiogenesis	VHL gene and protein	Dysregulated hypoxia inducible factor production	Increased VEGF and PDGFß with resultant classic angiogenic RCC phenotype	[Kaelin, 2009; George and Kaelin, 2003]
	VHL mutation	Loss of VHL protein production	Not prognostic but associated with disease stage may predict response to VEGF TKI therapy	[Choueiri *et al.* 2008; Brauch *et al.* 2000]
	HIF 1α and 2α	Increased levels lead to increased VEGF, EGF and PDGFβ; HIF2 appears responsible for inducing classic renal clear cell phenotype	High HIF levels in tumor tissues are required for response to sunitinib	[Kaelin, 2009; Patel *et al.* 2008]
	VEGF	Increased expression of VEGF and its receptor.	Increased stage	[Slaton *et al.* 2001; Dosquet *et al.* 1997; Takahashi *et al.* 1994; Brown *et al.* 1993]
		Increased VEGF	Poorer prognosis in some series	[Jacobsen *et al.* 2000].
Attenuated immune surveillance	T-cell immunity	Diminished activation, proliferation, and cytotoxic effect of T cells	Suppression of the hosts response to tumor; utilized in immunotherapeutic approaches	[Li and Verma, 2002; Finke *et al.* 2001; Kim *et al.* 1999; Uzzo et al. 1999a, 1999b; Grumont *et al.* 1998; Mcdonald *et al.* 1997]
	NF-kappaB	Broad immune dysfunction, interrupting cytokine-modulated coordination of B-lymphocytes, natural killer cells and neutrophils	Currently of questionable clinical or therapeutic significance but NF-kappaB remains a target of interest for drug development	[Li and Verma, 2002; Grumont *et al.* 1998; Mcdonald *et al.* 1997]
Altered regulation of transcription	Several including PTEN, akt, mTOR and S6 kinase	Aberration of the mTOR/akt/PTEN pathway	Increased cellular proliferation through dysregulated action of cyclins and c-myc as well as through hypoxia inducible factors important in the regulation of angiogenesis	[Hara *et al.* 2005; Atkins *et al.* 2004; Majumder *et al.* 2004; Brugarolas *et al.* 2003; Horiguchi *et al.* 2003]
			Expression of a variety of pathway components as predictive of survival in RCC	[Pantuck *et al.* 2007]
Signal transduction	EGF and EGF receptor-1	Over-expression	Higher tumor grade and inferior survival	[Hofmockel *et al.* 1997; Stumm *et al.* 1996; Uhlman *et al.* 1995; Gomella *et al.* 1990; Sargent *et al.* 1989]
Cell cycle regulation		Cyclin A over expression, $p27^{Kip1}$ loss and increased pRB expression	Adversely prognostic	[Migita *et al.* 2002; Haitel *et al.* 2001; Aaltomaa *et al.* 1999; Hedberg *et al.* 1999]
Apoptosis	p53	Frequent mutation or aberration	Inferior survival	[Sionov and Haupt, 1999; Oda *et al.* 1995; Reiter *et al.* 1993]
	Bcl-2	Frequent over expressed proto-oncogene	Inferior survival	[Gobé *et al.* 2002; Uchida *et al.* 2002; Haitel *et al.* 2001; Huang *et al.* 1999; Uhlman *et al.* 1994]
Extracellular matrix modulation	MMPs and their tissue inhibitors	Over expression of MMPs and/or TIMPs	Common in non-clear cell cancer and predict inferior survival	[Kallakury *et al.* 2001; Slaton *et al.* 2001]

EGF, epidermal growth factor; HIF, hypoxia inducible factors; MMPs, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; TIMPs, tissue inhibitor of metalloproteinases; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VHL, Von Hippel Lindau.

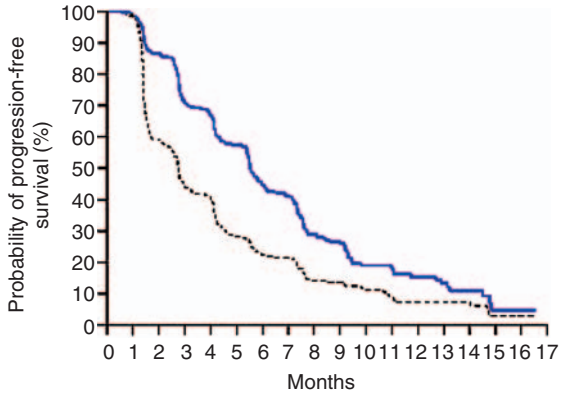


Figure 1. Sorafenib (blue line) *versus* placebo (black line) TARGET study progression-free survival curves for second-line good- and intermediate-risk renal cell cancer. After Escudier *et al.* [Escudier *et al.* 2007]. With permission, New England Medical Society.

patients [Hara *et al.* 2005; Atkins *et al.* 2004; Horiguchi *et al.* 2003].

Immune dysfunction

Deficits in tumor-directed T-cell immunity as well as cytokine-mediated effects on dendritic cells are characteristic of RCC [Li and Verma, 2002; Finke *et al.* 2001; Uzzo et al. 1999a, b; Kim *et al.* 1999; Grumont *et al.* 1998; Mcdonald *et al.* 1997; Li *et al.* 1994]. Factors which have been implicated in this immune dysfunction include nuclear factor kappa-β (NF-κB), which has a central role in coordinating the expression of a wide variety of genes that control immune responses in both T and B lymphocytes, natural killer cells and neutrophils [Li and Verma, 2002; Grumont *et al.* 1998; Mcdonald *et al.* 1997]. Agents that are immunostimulatory, such as interleukin-2 and interferon-α, have documented utility in RCC, although the exact mechanisms by which they exert their actions have been difficult to elucidate. One possible mechanism involves VEGF. Elevated VEGF-levels in tumor-bearing patients not only inhibit dendritic cell (DC) development from hematopoietic precursors but also decrease DC migration into tumors [Ohm *et al.* 2003; Gabrilovich *et al.* 1998; Oyama *et al.* 1998]. In mouse tumor models, the infusion of anti-VEGF antibodies results in a dramatic increase in the effectiveness of immunotherapy employing antigen-pulsed DCs [Li *et al.* 2002; Niethammer *et al.* 2002; Gabrilovich *et al.* 1999]. This suggests that therapies impacting VEGF, and perhaps other parts of the VEGF pathway, may help to reverse the immune dysfunction characteristic of RCC. This hypothesis remains to be tested in the clinical setting.

Recent analysis demonstrates significant clinical, pathological and molecular characteristics for non-clear RCC compared to clear cell RCC [Tamaskar *et al.* 2007; David *et al.* 2006; Ronnen *et al.* 2006; Upton *et al.* 2005; Dulaimi *et al.* 2004; Amin *et al.* 2002; Krishnan and Truong, 2002; Motzer *et al.* 2002]. The distinguishing molecular characteristics of non-clear RCC have recently been reviewed [Furge *et al.* 2007].

Advances in understanding of disease outcome based on clinical factors

For many years clinicians have recognized the heterogeneity of survival outcome in RCC. Recently revised pathological classification separates RCC into clear cell and non-clear cell types, the latter consisting of patients with papillary, chromophobe, oncocytoma and collecting duct tumors [Amin *et al.* 2002]. Each of these tumor types has a characteristic molecular profile [Takahashi *et al.* 2003] (see reviews) and a different clinical response to therapy [Ronnen *et al.* 2006]. Most particularly, it is important to note that only clear cell cancers respond to immunotherapy with cytokines while non-clear cases do not [Ronnen *et al.* 2006].

Major recent advances have been made in predicting outcomes for patients with advanced RCC, led by the Groupe Francais d'Immunotherapie, University of California Los Angles (UCLA), University of Padova and MSKCC [Bensalah *et al.* 2008; Escudier *et al.* 2007a; Karakiewicz *et al.* 2007; Patard *et al.* 2004a,b; Negrier *et al.* 2002; Zisman *et al.* 2001; Motzer *et al.* 2000, 1999]. Motzer and colleagues examined the survival rates for patients treated with interferon-α in a series of trials at MSKCC, and found that performance status, anemia, hypocalcaemia, elevated serum lactate dehydrogenase and duration from initial diagnosis to treatment for advanced or recurrent disease were predictive. In some models, the patients who had not undergone nephrectomy had a poorer outcome. Patients with none of these factors had a median OS of 22 months (good risk – around 20% of cases), 1 or 2 of these factors, a median survival of 11.9 months (intermediate risk – 65% of cases) and 3 or more

of these factors 5.4 months (poor risk – 15% of cases) [Motzer *et al.* 2004].

The MSK or 'Motzer classification system for advanced RCC has now been validated in a series of scenarios with excellent predictive value and subsequent trials have used this classification system to select and stratify patients for treatment. The first evidence of the importance of this approach came in the Groupe Francais d'Immunotherapie PERCY Quattro trial where intermediate risk patients were selected for supportive care with medroxyprogesterone acetate (MPA) or three combinations of low-dose chronic cytokine therapy [Negrier *et al.* 2007]. The study demonstrated no survival benefit to any of the cytokine regimens over supportive care centered on MPA. Recent reports suggest that the factors comprising the MSK score predict outcome for untreated patients and will likely be incorporated into nomograms to predict survival in patients treated with the newer targeted therapies [Motzer *et al.* 2008a; Mekhail *et al.* 2005], although alternative models are also under development. For instance, a Cox proportional hazards model using patients from nine trials of targeted therapy at the Cleveland Clinic identified a set of five different predictive variables: time from diagnosis to treatment, baseline neutrophil and platelet counts, ECOG performance status, and corrected serum calcium [Choueiri *et al.* 2007].

Before targeted agents – a brief history of renal cell cancer treatment

Early trials in advanced RCC focused on cytotoxic chemotherapy and hormonal treatments [Yagoda *et al.* 1995]. Cytotoxic therapy was rarely beneficial and does not appear to impact positively when added to cytokines or other agents [Ryan *et al.* 2002; Dutcher *et al.* 2000; Yagoda *et al.* 1995]. On the other hand, hormonal therapy with progestins (MPA or megestrol acetate) proved useful for ameliorating the symptoms of cancer-cachexia syndrome and, in the absence of specific anticancer effects in RCC, still has an important place in supportive care and palliation [Turner *et al.* 2007; Simons *et al.* 1996].

In the early 1980s, it became clear that patients with RCC had rare but major responses to immunomodulatory therapy with the human cytokines, interleukin-2 and interferon-α [Dutcher *et al.* 2001; Negrier *et al.* 2000a]. Subsequent trials demonstrated the ability of high-dose interleukin-2 to produce complete remissions in up to 15% of patients, with long-term durability in 80% of those who attained complete remission [Rosenberg *et al.* 1994]. Based on a series of phase II studies, the United States Federal Drug Agency (FDA) approved high-dose interleukin-2 for RCC [Rosenberg *et al.*, 1994]. However, the use of high-dose interleukin-2 comes at the cost of significant acute toxicity, which is entirely reversible, but nevertheless requires in-patient admission with access to intensive care facilities. Only patients with excellent performance status and no cardiorespiratory comorbities are suitable candidates because of the toxicity profile [Gitlitz *et al.* 2001; Fisher *et al.* 2000, 1988; Textor *et al.* 1987]. Regardless, given that high-dose interleukin-2 remains the only curative treatment for RCC, it remains an important treatment consideration, and continues to be offered in specialized centers to carefully selected patients. Work is underway in an attempt to better delineate patients likely to benefit from high-dose interleukin-2. Preliminary work suggested that overexpression of carbonic anhydrase IX in renal cancer tumor tissue increased the odds ratio of response to HD-IL2 by a factor of approximately three [Atkins *et al.* 2005]. The high-dose interleukin-2 'SELECT' trial for metastatic RCC is ongoing within the Cytokine Working Group with the aim of prospectively validating carbonic anhydrase IX expression and search for other markers of response with the potential to exclude patients who are very unlikely to benefit from this therapy [Mcdermott *et al.* 2009].

Given the limited applicability of high-dose interleukin-2, outpatient subcutaneous cytokine regimens were developed using either interleukin-2, interferon-α or a combination of both [Figlin *et al.* 1992; Rosenberg *et al.* 1989; Fisher *et al.* 1988]. A series of trials were undertaken with these combinations. Importantly, cytokines were superior to therapy with the cytotoxic agents such as vinblastine or paclitaxel [Yagoda *et al.* 1995; Walpole *et al.* 1993]. Other studies suggested delay in disease progression for combined low-dose therapy compared to single agent treatment, although this never translated to OS benefit [Negrier *et al.* 2000b, 1998]. The addition of low-dose interferon-α to interleukin-2 was not advantageous [Atkins *et al.* 1993] nor was infusion of tumor-infiltrating lymphocytes

extracted from the primary renal cancer at time of nephrectomy [Figlin *et al.* 1999].

A meta-analysis and systemic review of immunotherapy in RCC was undertaken for the Cochrane database in 2000 and updated in 2005 [Coppin *et al.* 2005]. This review concluded that immunotherapies resulted in a partial or complete response rate of 12.9% compared to 2.5% in nonimmunotherapy controls and 4.3% in placebo controls. The median OS benefit attributed to immunotherapy was 3.8 months compared to controls. Moreover, there was limited correlation of response with survival. These conclusions emphasized the limited effect of interferon-α over best supportive care, (incorporating MPA) seen in the MRC trial where the difference in median OS was 2.8 months [Collaborators, 1999]. This review also noted that nephrectomy in metastatic RCC patients given interferon-α resulted in a median 4.8 month improvement in OS [Flanigan *et al.* 2001; Mickisch *et al.* 2001].

Subsequently, two important randomized trials of immunotherapy were undertaken. A comparison of high-dose interleukin-2 and low-dose subcutaneous interferon-α and interleukin-2 in combination demonstrated superior response rates for high-dose interleukin-2 and poorer quality-of-life for patients given the low-dose combination regimen [Mcdermott *et al.* 2005]. Most recently with improved clinical categorization of patients into risk groups, the Groupe Francais undertook the PERCY (Programme Etude Rein Cytokines) Quattro trial comparing MPA, interferon-α alone, interleukin-2 alone or a combination of interleukin-2 and interferon-α in patients with intermediate-risk clear cell carcinoma [Negrier *et al.* 2007]. The OS outcomes for all arms were not different to supportive care offered as the control arm with MPA. In addition, in quality-of-life evaluation, treatment with either cytokine resulted in further decrement compared to MPA and the combination arm was even worse. This suggests that when low-dose cytokines are given to this selected population of RCC patients with intermediate-risk disease (which comprises 60–70% of patients seen) there is no effect on survival, despite significant morbidity. On this basis low-dose subcutaneous regimens are now limited to combination with targeted agents (see below) or use solely in patients with good-risk disease who are not suitable for high-dose interleukin-2, who have declined or are unsuitable for targeted therapy.

Sorafenib

Sorafenib (BAY 43-9006, Nexavar®), a dual-specificity multikinase inhibitor, inhibits both tyrosine and serine/threonine-specific kinases, and has been implicated as an inhibitor of kinase targets involved at different levels of the cascade [Wilhelm *et al.* 2004]. Biochemical assays have demonstrated that sorafenib inhibits the autophosphorylation of VEGFR-2 and -3 and PDGFRβ, c-KIT and FMS-like tyrosine kinase-3 (FLT-3) and, further, can inhibit the kinase activity of the serine/threonine kinases, c-Raf, BRaf, and p38MAPK (see Figure 1)[Wilhelm *et al.* 2004]. This repertoire suggests sorafenib is a potential inhibitor of tumorigenic signaling in both endothelial cells and tumor cells.

Two phase I studies defined sorafenib 400 mg, taken orally twice daily on a continuous basis, as a tolerable dose with a high rate of disease stability [Awada *et al.* 2005; Strumberg *et al.* 2005], while a third trial suggested that higher doses of 600 mg or even 800 mg twice daily were tolerable in many patients [Clark *et al.* 2005]. Initially felt to act predominantly through the raf kinase pathway, it soon became evident that the major effect for sorafenib was through VEGF receptor inhibition. A phase II, placebo-controlled trial of sorafenib, 400 mg twice daily, using a randomized discontinuation of treatment (RDT) design was undertaken [Ratain *et al.* 2004; Rosner *et al.* 2002]. A total of 202 metastatic RCC patients were treated for 12 weeks with sorafenib and 71% demonstrated a response or had stabilized disease. Patients with a 25% reduction in measurable disease were deemed responders and continued on sorafenib while those whose disease had progressed with a 25% or greater increase in disease ceased treatment. Patients with stable disease were offered randomization and 65 consented to this. Patients continuing treatment with sorafenib had four times longer PFS compared to patients that were randomized to stop the drug (24 *versus* 6 weeks, $p = 0.0087$)[Ratain *et al.* 2006].

After the results of the RDT trial became available, the decision was made to design TARGET (Therapeutic Approaches in Renal Cancer Global Evaluation Trial), a large randomized trial of sorafenib given at a dose of 400 mg twice daily orally on a continuous basis compared

to placebo [Escudier *et al.* 2007b]. The study population was selected to have clear cell histology, failed at least one therapy within 8 months of enrolment, good performance status and measurable disease. The study enrolled 905 patients with low- or intermediate-MSKCC risk advanced disease who had received prior systemic therapy; patients with brain metastases or poor risk stratification were excluded. The major endpoints were OS and PFS. Although only one patient had a complete response and 10% qualified as partial response according to investigator reported RECIST criteria (Response Evaluation Criteria in Solid Tumors), about 75% had some shrinkage in their tumors compared to 25% of those in the placebo group. This relatively subtle change in tumor growth kinetics yielded a dramatic difference in PFS, which was doubled from 12 weeks in the placebo group to 24 weeks in the sorafenib group (Hazard ratio (HR) 0.44, 95% confidence interval (CI) 0.35–0.55, $p < 0.00001$, see Figure 1, Table 2).

Given the clear advantage of sorafenib at this first planned PFS analysis, it was decided on ethical grounds to allow patients in the placebo arm to crossover to active treatment. This crossover impacted 215 patients in the placebo arm and necessitated a change in the trial design to evaluate OS: crossover patients were censored as 'not relapsed' at the point of crossover but with no further follow up taken into account. In this analysis, OS in the placebo group was 14.3 months, while median survival in the sorafenib group was 17.8 months (HR 0.78, 95% CIs 0.62–0.97, $p = 0.0287$) [Escudier *et al.* 2009a; Bukowski *et al.* 2007a]. The median OS benefit in favour of sorafenib was approximately 3.5 months; an important finding for this drug with implications for the potential benefits of other angiogenesis inhibiting agents in RCC.

Subsequently, sorafenib was evaluated in untreated patients with RCC in a two-arm first-line randomized phase II trial with interferon-α as the comparator arm [Escudier *et al.* 2009]. While conclusions from such studies can be difficult to interpret, there was no difference in median PFS between the arms, a result that stands in contrast to the phase III trial comparing sunitinib with interferon-α in the same setting [Motzer *et al.* 2007]. Sorafenib did have a superior response rate and quality-of-life profile compared to interferon-α [Escudier *et al.* 2009b].

Table 2. Randomized phase III trial of sorafenib compared to placebo for renal cell cancer patients progressing on prior, predominantly cytokine, therapy [Escudier *et al.* 2009a, 2007b].

Treatment	PFS	*p* value	OS	*p* value
Sorafenib	5.5	<0.0001	17.8	0.029
Placebo	2.8		14.3	

OS, overall survival, PFS, progression-free survival.

Overall, sorafenib has a favourable safety profile. In the TARGETs trial the incidence of any grade 3–4 adverse event was 30% in sorafenib-treated patients and 22% in the placebo group [Escudier *et al.* 2007b]. Common adverse events recorded for the sorafenib group were hypertension, a known effect of inhibition of VEGFR signalling, hand-foot syndrome, fatigue, and diarrhea. Despite these side effects, sorafenib was associated with an improved quality of life compared to placebo in this trial [Bukowski *et al.* 2007c].

The range of sorafenib side-effects in clinical practice outside of a trial setting is similar to that seen in the clinical trials, although the incidence may vary. For instance, more patients may develop hypertension after nephrectomy, due to limited residual renal function. The mechanism of blood pressure elevation is not clear, but one study demonstrated an increase in systolic blood pressure of 10 mm Hg in 75% of cases, with 60% of patients experiencing an increase >20 mm Hg [Veronese *et al.* 2006]. Nevertheless, this can be managed with careful home blood pressure monitoring and the adjustment of ongoing antihypertensive agents or the addition of new ones; to date there is no preferred class of antihypertensive drug for this indication. The most common toxicity with sorafenib is hand-foot skin syndrome and rash, which can occur with varying severity in 60–70% of patients. Even in severe cases, however, most patients can continue treatment after temporary cessation of the drug has facilitated resolution of the symptoms. Lanolin-based emollient creams applied twice daily can help control skin reactions; urease-containing emollients can also be helpful. Diarrhea is a third common adverse event. There are two broad types: one that is an increased frequency, which can be managed with anti-diarrheal agents, and the other which is more sporadic, unpredictable and explosive, which patients need to be warned about. Interestingly, the presence of skin toxicity or diarrhea correlates with increased

time-to-progression compared to patients that do not experience these side effects [Strumberg *et al.* 2006].

Sorafenib has also recently been approved for hepatocellular carcinoma after the completion of an international phase III trial demonstrating superior OS compared with placebo [Llovet *et al.* 2008].

Sunitinib

Sunitinib (SU11248, Sutent®) is a multiple kinase inhibitor with activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, c-kit, and Flt-3 [Rini and Small, 2005]. *In vitro* data indicated that sunitinib could block VEGF-induced endothelial proliferation as well as PDGF-induced proliferation of murine fibroblasts [Mendel *et al.* 2003]. Mice injected with human melanoma and glioma cell lines demonstrated *in vivo* that sunitinib treatment could block VEGFR- and PDGFR-mediated signaling cascades [Sun *et al.* 2003]. More importantly, treatment with sunitinib inhibited growth of xenografts in mice, and eradicated established tumors. After treatment, immunohistochemical staining for CD31 in xenograft sections revealed that microvessel density was reduced [Sun *et al.* 2003]. Sunitinib's activity in suppressing angiogenesis and cell proliferation in the preclinical setting was significant enough to warrant further investigation [Osusky *et al.* 2004; Abrams *et al.* 2003].

A phase I study established a tolerable dose for sunitinib of 50 mg daily orally for 28 days followed by a 14-day break, where attempts at continuous dosing proved too toxic [Faivre *et al.* 2006]. Analysis of two single arm phase II trials of sunitinib as second-line therapy in patients who had prior cytokine failure revealed that it had substantial anti-tumor activity in this setting [Motzer *et al.* 2006a, 2006b]. A total of 169 patients were treated with a regimen of 50 mg of daily oral therapy given for 4 weeks, repeated in 6-week cycles. A combined objective response rate of approximately 40% and disease stabilization in 25% was reported, with an associated median PFS of 8.8 months and median OS of 24 months [Motzer *et al.* 2007a, 2006a, 2006b].

To evaluate the efficacy of sunitinib in treatment naïve patients with metastatic RCC, an international phase III trial was conducted with thrice weekly interferon-α as the comparator arm [Motzer *et al.* 2007b]. Seven hundred and fifty patients with metastatic clear cell RCC were randomized in a 1:1 ratio to interferon-α or sunitinib 50 mg daily, 4 weeks on then 2 weeks off. While no patients in the trial had a complete response, more patients receiving sunitinib achieved partial response (31%) than those in the interferon-α arm (6%). The rates of stable disease in the treatment groups were similar; 48 and 49% for sunitinib and interferon-α respectively, but fewer patients receiving targeted therapy had progressive disease. Similar to the results seen with sorafenib in the second-line setting, there was a doubling of PFS in the sunitinib group (11 months) compared to the control group (5.1 months) (HR 0.538, 95% CIs 0.439–0.658, $p < 0.00001$) (Figure 2, Table 3). OS data show a median survival of 26 months in the sunitinib arm compared to 21 in the interferon-α arm [Motzer *et al.* 2009]. The difference has marginal statistical significance ($p = 0.051$, HR = 0.821; 95% CI, 0.673–1.001); however, given the large number of patients who receive active drugs such as sorafenib after failing interferon-α, one can hypothesize that the survival difference in the trial was diluted by this effect.

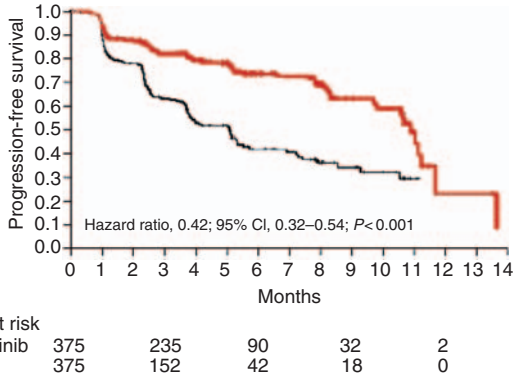


Figure 2. Sunitinib (red line) *versus* interferon-α (IFN, black line) study progression-free survival curves for first-line renal cell cancer [Motzer *et al.* 2007]. With permission, New England Medical Society. CI, confidence interval.

Table 3. Randomized phase III trial of sunitinib compared to interferon-α in advanced renal cell cancer patients not having prior systemic therapy [Motzer *et al.* 2009, 2007b].

Treatment	PFS	*p* value	OS	*p* value
Sunitinib	11	<0.001	26.4	0.051
Interferon-α	5		21.8	

OS, overall survival, PFS, progression-free survival.

Post-hoc analyses excluding patients who received any targeted therapy after study therapy with either sunitinib or interferon-*α*, did demonstrate substantive differences in OS that many feel reflect a true advantage for sunitinib.

Treatment with sunitinib was well tolerated over a long period of time in some patients, with fewer than 10% of patients experiencing grade 3–4 toxicity, though 50% required a dose reduction. Grade 2–3 treatment-related adverse events noted during sunitinib trials included fatigue, diarrhea, stomatitis, nausea and hypertension. Hand-foot syndrome was far less commonly seen than with sorafenib [Robert *et al.* 2005]. Laboratory abnormalities described for sunitinib treated patients were neutropenia, anemia, and thrombocytopenia. There was a 13% incidence of left ventricular dysfunction in the sunitinib arm compared to 3% with interferon-*α* [Motzer *et al.* 2007b] and patients treated with sunitinib should be monitoring with echocardiography or nuclear-labeled LVEF assessment at baseline and periodically during treatment [Khakoo *et al.* 2008; Telli *et al.* 2008; Chu *et al.* 2007]. Thyroid function anomalies are also common with sunitinib therapy, with hypothyroidism being relatively common and transient hyperthyroidism reported [Rini *et al.* 2007]. Routine monitoring of serum thyroid stimulating hormone levels is now undertaken in most centers. Another idiosyncratic side effect of sunitinib is hair depigmentation, the nature of which varies with patient race [Faivre *et al.* 2006].

Sunitinib has also recently been approved for the treatment of gastrointestinal stromal tumors that are refractory to first line therapy with imatinib [Demetri *et al.* 2006].

Bevacizumab

Bevacizumab (Avastin®), a recombinant human monoclonal antibody against VEGF isomer A (see Figure 1), was the first targeted agent to show efficacy in RCC. In a phase II study, high-dose bevacizumab (10 mg/kg IV every 2 weeks) doubled the time-to-progression compared with placebo (4.8 months *versus* 2.5 months, $p < 0.001$) in patients with metastatic RCC who had progressed on high-dose interleukin-2 [Yang *et al.* 2003]. These data were promising, but to prove the benefit a very large phase III study was required, which was not initially feasible. However, subsequent trials incorporating bevacizumab in combination with interferon-*α* have now been completed [Rini *et al.* 2008; Escudier *et al.* 2007c]. These trials, the AVOREN (Roche B017705) trial and the CALGB-90206 trial, were launched in the absence of formal phase I testing but incorporated safety evaluations to identify potential significant toxicity of the combinations.

The AVOREN trial selected treatment-naïve patients with RCC to be randomized to interferon-*α* with either intravenous (IV) bevacizumab, 10 mg/kg, or placebo every 2 weeks. Interferon-*α* was given at a dose of 9 million units (MU) subcutaneously, thrice weekly [Escudier *et al.* 2007c]. The combination arm showed a markedly better response rate of 31% compared to 13% in the interferon-*α* plus placebo arm ($p < 0.0001$). Median PFS was 10.2 months for interferon-*α* with bevacizumab and 5.4 months for interferon-*α* with placebo ($p < 0.0001$; Figure 3a, Table 4). Toxicities and adverse events were similar between the two arms, although patients getting bevacizumab were more likely to experience hypertension and/or proteinuria.

In the CALGB-90206 trial, the design and patient selection were similar to AVOREN except that patients were not given placebo infusions in the control arm and therefore patients and clinicians were aware of which patients were receiving bevacizumab [Rini *et al.* 2008]. The combination arm showed better response rate of 26% compared to 13% in the interferon-*α* alone arm ($p < 0.0001$; Figure 3b, Table 4). Median PFS was 8.5 months for interferon-*α* with bevacizumab and 5.2 months for interferon-*α* alone ($p < 0.0001$). Toxicities and adverse events were similar between the two arms, although patients who received bevacizumab were more likely to experience hypertension, anorexia, fatigue and/or proteinuria. Full analysis for OS effect, which was the primary endpoint in both trials, awaits further follow up. These response and PFS data attest to the additive effect for bevacizumab in addition to interferon-*α*. Prior phase II studies have reported similar data for single-agent bevacizumab [Bukowski *et al.* 2007b] A retrospective analysis of the AVOREN trial found that patients who had dose reductions of interferon-α for toxicity had no detriment in PFS [Melichar *et al.* 2008]. This is hardly definitive, but suggests that lower dose interferon-*α* with bevacizumab may be an option. The question of whether single-agent

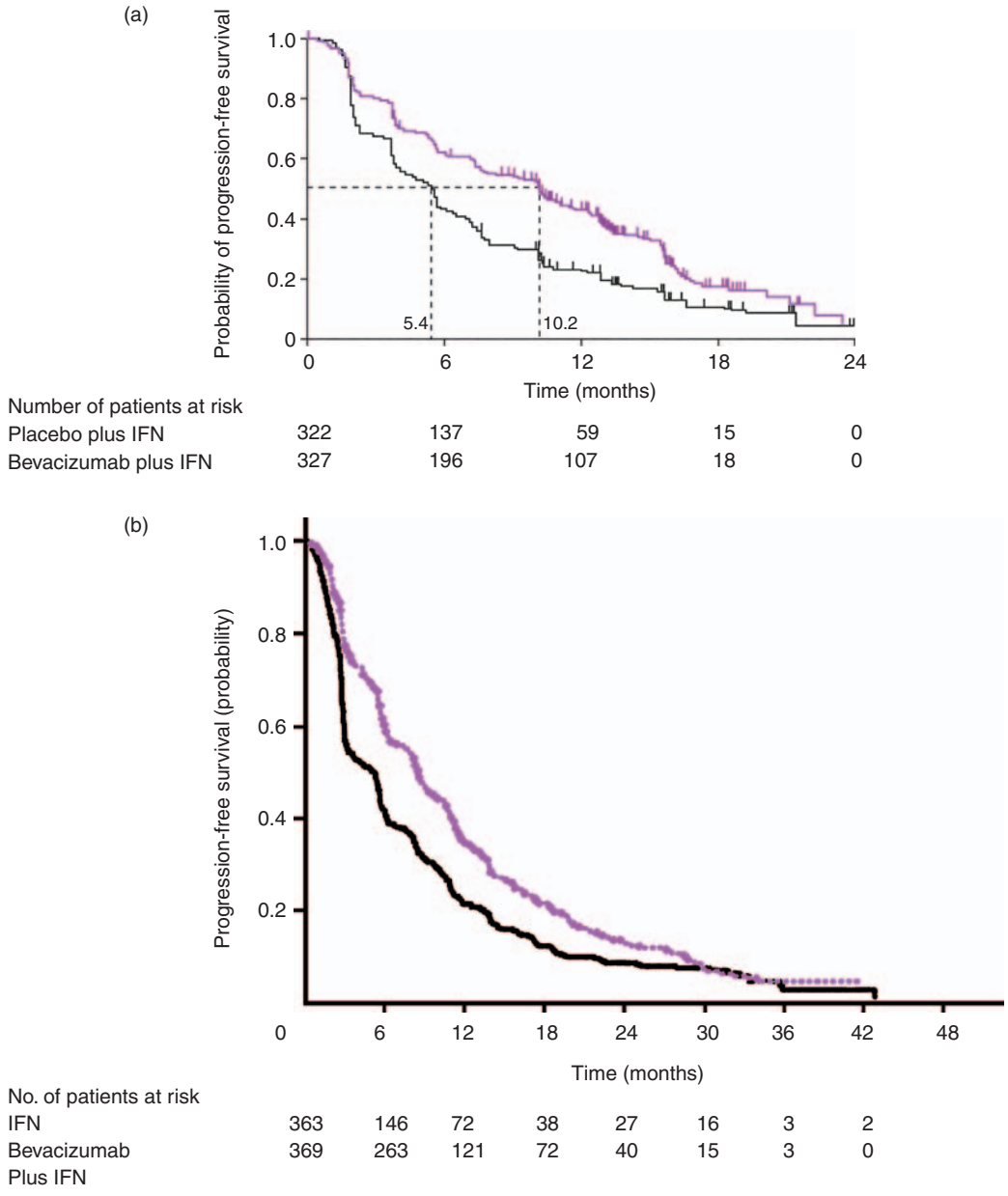


Figure 3. (a) Interferon-α (IFN) with placebo (black line) *versus* IFN with bevacizumab (purple line) in untreated patients with recurrent or advanced renal cell carcinoma – AVOREN Trial – progression-free survival [Escudier *et al.* 2007c]. With permission, *The Lancet*, (b) Interferon-α (IFN) alone (black line) and with bevacizumab (purple line), in untreated patients with recurrent or advanced renal cell carcinoma – CALGB Trial 90206 – progression-free survival [Rini *et al.* 2008]. With permission, American Society for Clinical Oncology.

bevacizumab given in the absence of interferon-α could produce similar outcomes to the combination remains unresolved and will require additional trials.

Bevacizumab is approved for the treatment of advanced colorectal cancer and advanced non-small cell non-squamous histology lung cancer in combination with chemotherapy [Sandler *et al.* 2006; Hurwitz *et al.* 2004].

Temsirolimus

Temsirolimus (CCI-779, Torisel®) is an ester of rapamycin, which inhibits mTOR (mammalian Target Of Rapamycin), regulates cellular glucose homeostasis and inhibits production of VEGF through direct and indirect effects on hypoxia-inducible factor. In addition, the drug mediates proliferation through cyclin and c-myc, at least partially through regulation of S-6 kinase activity [Guba *et al.* 2002; Dudkin *et al.* 2001].

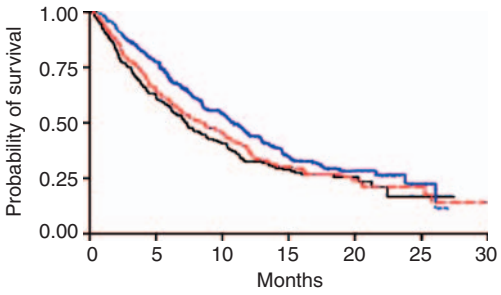
Table 4. Randomized phase III trials of interferon-α with or without bevacizumab in advanced renal cell cancer patients not having prior systemic therapy [Rini *et al.* 2008c; Escudier *et al.* 2007c].

Treatment	PFS	*p* value	OS	*p* value
AVOREN Study				
Interferon-α + bevacizumab	10.2	0.0001	NR	NA
Interferon-α	5.4		19.8	
CALGB 90206				
Interferon-α + bevacizumab	8.5	0.0001	NR	NA
Interferon-α	5.2		NR	

NR, not reached; OS, overall survival, PFS, progression-free survival.

A randomized phase II trial investigated the efficacy of temsirolimus over a range of doses administered on a weekly schedule (25, 75, or 250 mg) in 111 patients with refractory, advanced RCC [Atkins *et al.* 2004]. An overall response rate of 7% and a minor response rate of 26% were observed. The median survival was 15 months, and the median observed time-to-progression was 5.8 months. Importantly, the investigators noted that patients who entered this trial who were in the MSKCC poor-risk category had a better than expected OS of around 8 months compared to a predicted median of 5 months. Phase I data suggested that temsirolimus and interferon-α could be given together but required reduced doses due to stomatitis, fatigue and nausea/vomiting [Motzer *et al.* 2007c].

Subsequently, a phase III trial was undertaken, which randomized 626 patients with largely poor-risk, but also some intermediate-risk, metastatic RCC between three arms: interferon-α (up to 18 MU subcutaneously three times/week), temsirolimus (25 mg IV weekly) or temsirolimus (15 mg IV weekly) plus interferon-α (6 MU subcutaneously three times/week). Distinct from the sorafenib and sunitinib trials, non-clear cell histological subtypes were not excluded [Hudes *et al.* 2007]. This trial demonstrated that temsirolimus alone conferred a survival benefit (Figure 4, Table 5) compared to temsirolimus plus interferon-α or interferon-α alone [Hudes *et al.* 2007]. However, both the temsirolimus plus interferon-α-group and the temsirolimus-alone group performed similarly in terms of PFS, suggesting that temsirolimus elongates the time to progression and OS, while the addition of interferon-α does not provide translation of the improved PFS (compared to interferon-α alone)



No. at risk

Interferon	207	126	80	42	15	3	0
Temsirolimus	209	159	110	56	19	3	0
Combination	210	135	93	50	17	7	2

Figure 4. Temsirolimus (blue line) *versus* temsirolimus and interferon-α (IFN, red line) *versus* IFN alone (black line) in first-line poor-risk renal cell cancer patients — overall survival [Hudes *et al.* 2007]. With permission, New England Medical Society.

Table 5. Randomized phase III trial of temsirolimus, interferon-α or both in poor-risk metastatic renal cell cancer patients [Hudes *et al.* 2007].

Treatment	PFS	*p* value	OS	*p* value
Temsirolimus	3.7	0.0001	10.9	0.0069
Interferon-α	1.9	0.0019	7.3	0.6912
Interferon-α + temsirolimus	3.7		8.4	

OS, overall survival, PFS, progression-free survival.

into better OS. Similar objective responses were observed in 7, 9, and 11% of patients in the interferon-α, temsirolimus, and combination arms, respectively. This trial has been the subject of criticism. The use of interferon-α as the standard therapy arm is considered inappropriate by some, in the context that cytokine therapy does not benefit patients with poor-risk features. In addition, accrual was relatively slow to the trial given the rarity and fragility of poor-risk patients being recruited. On this basis, eligibility criteria were broadened to allow patients into the trial who had multiple sites of metastatic disease. The result was improved accrual with addition of patients who fell strictly into the MSKCC intermediate-risk category. A yet-to-be-published post-hoc analysis of this trial demonstrated that the benefit of temsirolimus over interferon-α only occurred in patients with poor-risk MSKCC disease, with no benefit in intermediate-risk disease. This same post-hoc analysis demonstrated that patients with non-clear cell RCC benefited from temsirolimus while those with clear cell histology did not and that patients less than 65 years old at

study entry benefited from temsirolimus while old patients did not. The implications of these findings for clinical practice are unclear but provocative enough to rate consideration in particular patients.

Significant grade 3 toxicities reported for patients treated with temsirolimus given as 25 mg IV each week were mucositis, thrombocytopenia, hypophosphatemia, leucopenia, anemia, asymptomatic hyperlipidemia, hyperglycemia and skin and nail toxicities. Notably, asthenia was more common in patients receiving interferon-*a*, while rash was more common the temsirolimus arm.

Temsirolimus is now considered a standard for patients with poor risk metastatic RCC. The role of this drug and other mTOR inhibitors in other RCC settings and in other tumor types is under investigation.

Everolimus

Everolimus, an esteric derivative of rapamycin with some structural homology with temsirolimus, binds to an intracellular protein, FKBP-12, forming a complex that inhibits the mTOR serine-threonine kinase. Its effects are mediated through hypoxia-inducible factors to angiogenesis and S-6 kinase for cell cycle regulation.

Pharmacodynamic-pharmacokinetic modeling of dose and dose scheduling based on plasma sirolimus levels and inhibition of patients peripheral blood lymphocytes of S6 kinase, suggested that the optimal tumor kill would occur with daily dosing of the everolimus [O'Donnell *et al.* 2008; Tanaka *et al.* 2008]. In one phase I study, initial weekly dosing schedules were explored but pharmacodymanic data led to the trial being amended to incorporate daily dosing. This eventually led to optimal dosing at 10 mg/day orally for moving forward into later phase trials. The study recorded four partial responses and 12 patients with protracted stable disease. Of ten RCC patients treated, five had protracted response or stable disease. The daily dosing schedule of everolimus was further explored in a phase I/II study in patients with hematological disorders [Yee *et al.* 2006].

Subsequently, the RECORD-1 trial was designed to evaluate oral daily everolimus compared to placebo in patients who had failed one or both of the approved VEGF TKIs (TKIs), sorafenib and/or sunitinib [Motzer *et al.* 2008b]. Patients were permitted to have had other therapies apart from a VEGF TKI, such as cytokines, chemotherapy or bevacizumab. The trial accrued 410 patients randomized in a 2:1 ratio to everolimus and placebo. At interim analysis the trial was halted because the median PFS in everolimus was 4.1 months compared to 1.9 months in the placebo group, (HR 0.30, 95% CI 0.22–0.40, $p < 0.0001$). Only one person in the everolimus groups achieved a partial response but 65% of patients on placebo progressed compared to 37% on everolimus (Table 6, Figure 5).

Overall everolimus therapy was well tolerated. A small number of patients developed pneumonitis on everolimus, a side effect seen with other agents in this class, which responded to a break in therapy and institution of corticosteroids in symptomatic cases. Stomatitis, rash and fatigue were more common in the everolimus group compared with the placebo group. Everolimus is the first drug to demonstrate a PFS benefit for patients who are no longer responding to VEGF TKIs. Patients will be followed up in the coming months to determine whether there is a survival advantage.

Table 6. Randomized phase III trial of everolimus with best supportive care or placebo with best supportive care in metastatic renal cell cancer patients who have failed at least one vascular endothelial growth factor tyrosine kinase inhibitor [Motzer *et al.* 2008b].

Treatment	PFS	*p* value	OS	*p* value
Everolimus	4.0	0.0001	NR	NA
Placebo	1.9		8.8	

NR, not reached; OS, overall survival, PFS, progression-free survival.

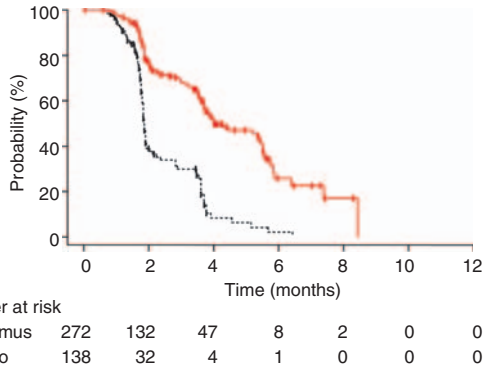


Figure 5. Everolimus (red line) compared to placebo (black line) on patients who have progressed on at least one vascular endothelial growth factor tyrosine kinase inhibitor – RECORD-1 Trial [Motzer *et al.* 2008b]. With permission, *The Lancet*.

The potential roles of everolimus prior to VEGF TKI treatment, in the adjuvant setting and in non-clear cell histologies are the subject of several accruing or planned clinical trials.

Sequencing of targeted drugs in renal cell cancer

Given the activity of newer agents targeting either VEGF or mTOR in advanced RCC, the potential benefit or toxicity of sequential or combination therapy raise obvious questions [Hutson and Figlin, 2007].

The selection of first-line therapy has become extremely complex. Pre-therapy predictors of outcome are lacking and leave much to the clinician's judgement and the therapeutic aspirations of an individual patient. Options are summarized in Table 7 related to levels of evidence for different MSK categories in first-line and for the prior therapy failed subsequently. Generally, first-line patients should be offered sunitinib, which has activity across all three MSK categories, although there is strong data for the use of temsirolimus in poor-risk patients and potential for cure in a small fraction of patients with good-risk disease given high-dose interleukin-2 [Hutson and Quinn, 2005]. Patients might also be offered bevacizumab and interferon-α or potentially sorafenib if they have evidence of cardiac failure or other vascular risk factors [Telli *et al.* 2008; Chu *et al.* 2007]. A clinical trial always remains a good option for every patient.

For patients failing first-line therapy, phase III data supports the use of sorafenib for patients failing cytokine therapy and everolimus for patients failing VEGF TKIs [Motzer *et al.* 2008b; Escudier *et al.* 2007a]. There is also phase II data demonstrating activity for sunitinib in this setting. A potentially important issue relates to how an individual fails therapy.

(1) Patients developing progressive disease on full doses of a VEGF TKI may be more likely to have VEGF-pathway resistance and less likely to respond to another VEGF-pathway therapy. Logic might suggest that they would be better served by being treated with an agent that has a different mechanism of action such as an mTOR modulator.
(2) Patients who stop therapy with a VEGF TKI because of toxicity, or reduce dose of the drug because of side effects, and then progress are less likely to have VEGF-pathway resistance. They may be candidates for further VEGF-pathway targeted therapy with agents that have a different profile of side effects and toxicities.

To address these issues, accruing studies will compare mTOR modulation to further VEGF TKI therapy (STAR Trial) and different VEGF TKIs for patients failing first-line therapy (AXIS Trial) [Rini, 2008a; Hutson, 2007]. In addition, another study will examine the effect of commencing therapy with either sunitinib (considered a first-line standard in many clinician's eyes) or sorafenib and switching to the other at progression or intolerance with total time-to-progression on the second VEGF TKI as a major endpoint.

Combination therapy with targeted drugs

Efforts at combining targeted agents with one another and with cytokine therapy have met

Table 7. Summary of evidence-based approach to therapy for advanced or recurrent renal clear cell carcinoma in 2009 (Adapted from Rini B, American Society for Clinical Oncology Annual Meeting 2008 [Rini, 2008b]).

Setting	Patients	Therapy (level 1)	Other options (≥ level 2)
Untreated	Good or intermediate MSK risk	Sunitinib [Motzer *et al.* 2007b] Bevacizumab + IFN [Rini *et al.* 2008; Escudier *et al.* 2007c] Clinical trial	HD IL-2 [Fisher *et al.* 2000] Sorafenib [Ratain *et al.* 2006] Clinical trial observation
Untreated	Poor MSK risk	Temsirolimus [Hudes *et al.* 2007a] Clinical trial	Sunitinib [Motzer *et al.* 2007a] Clinical trial
Refractory	Cytokine	Sorafenib [Escudier *et al.* 2007a] Pazopanib [Hutson *et al.* 2007b] Clinical trial	Sunitinib [Motzer *et al.* 2006], Bevacizumab [Bukowski *et al.* 2007b]
Refractory	VEGF; mTOR	Everolimus[Motzer *et al.* 2008b] Clinical trial	Other VEGF TKIs Axitinib [Dutcher *et al.* 2008; Rixe *et al.* 2007]

IFN, interferon; MSK, Memorial Sloan Kettering; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

with limited success, mainly because of toxicity. The addition of bevacizumab to VEGF TKIs has been difficult due to vascular toxicity, most commonly hypertension, but on occasion renal failure and central nervous system vaso-occlusive phenomena, and hand-foot syndrome [Feldman *et al*. 2009]. Early phase trials combining mTOR inhibitors with VEGF pathway directed drugs look to provide a better toxicity profile. Combinations of sorafenib, bevacizumab and temsirolimus will be evaluated by the North American Cooperative Groups in the BEST trial [Flaherty *et al*. 2007]. Combination of VEGF-directed agents with cytokines therapies also look promising as evidenced by the combination of bevacizumab and interferon-α in the AVOREN and CALGB trials. Combination of interferon-α with VEGF TKIs does appear to increase response but at the cost of increased toxicity which is considerable in some cases [Bracarda *et al*. 2007; Gollob *et al*. 2007; Jonasch *et al*. 2007; Ryan *et al*. 2007].

Adjuvant therapy after nephrectomy for high-risk renal cell cancer

As many as 50% of patients treated with curative intent for localized RCC will relapse. Risk of relapse is predicted by cancer nuclear grade, disease stage and performance status in the University California Los Angeles integrated staging system (UISS) [Karakiewicz *et al*. 2007; Zisman *et al*. 2001]. Symptomatic presentation as opposed to incidental diagnosis also has an adverse impact on outcome [Patard *et al*. 2004]. Given the high rate of relapse for certain identifiable groups, adjuvant therapy appears a logical approach. Unfortunately, no treatment represents a standard intervention in the adjuvant setting in RCC. Previously the Eastern Cooperative Oncology Group (ECOG) led a trial of the use of interferon-α for a year after nephrectomy compared to observation. This trial found that patients given interferon-α had a trend toward a worse survival ($p = 0.09$) and a poor quality-of-life during treatment [Messing *et al*. 2003]. High-dose interleukin-2 therapy has also failed to demonstrate benefit in this setting, although data are limited. The Cytokine Working Group evaluated the potential of one course of high-dose interleukin-2 therapy compared to observation in the adjuvant setting; this underpowered study failed to suggest an advantage over observation [Clark *et al*. 2003].

Current trials are examining the potential of newer TKIs such as sorafenib and sunitinib in the adjuvant setting for patients at high risk of relapse [Yap and Eisen, 2006]. ECOG Trial E2805, also known as ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) will accrue 1,736 patients with locally advanced clear cell RCC treated with nephrectomy to one year of therapy with sorafenib or sunitinib or placebo, with a primary endpoint of OS. This trial is accessible through ECOG, SWOG, CALGB and NCI Canada [Balzer-Hass *et al*. 2007]. In Europe, the SORCE trial will examine the use of one of year of sorafenib, three years of sorafenib or placebo in a similarly selected group of patients [Eisen, 2007]. It will answer a further question about the duration of adjuvant therapy for these patients. Other adjuvant trials are planned, including one comparing the mTOR inhibitor, everolimus, given for one year *versus* placebo.

Given that our experience with sorafenib and sunitinib is still relatively limited, we need to be vigilant for chronic side-effects in patients on long-term treatment. This is especially applicable to patients getting adjuvant treatment after surgery on a range of ongoing trials, where dose maintenance and compliance have been more problematic than for patients with advanced disease on the same regimen.

New targeted agents for renal cell cancer

The plethora of targeted agents coming to trials and being licensed in the last 3 years represents only the first wave of agents for these groups. It is likely that as many as a dozen VEGF pathway and six mTOR/akt modulators could be marketed for RCC in the next several years. A detailed overview of these agents is outside the scope of this current article but has recently been skillfully reviewed by Sonpavde and Hutson [Sonpavde and Hutson, 2008]. Two agents are, however, worthy of note. Pazopanib, a VEGF TKI [Hurwitz *et al*. 2009], has been evaluated in a large phase II trial in RCC patients with encouraging tumor response rate and a median OS of around 11 months for patients not previously treated for advanced disease [Hutson *et al*. 2007]. This compares favourably with other agents licensed for use in RCC. A recently presented phase III trial demonstrated a significant PFS advantage compared to placebo for first-line patients and also for those who had previously been treated with cytokines

[Sternberg *et al.* 2009]. Axitinib, another VEGF TKI, has shown significant activity in a phase II trial of cytokine refractory patients [Rixe *et al.* 2007] and also appears to have activity in patients progressing on other targeted agents [Dutcher *et al.* 2008]. It is currently being compared to sorafenib in a phase III trial for patients who have progressed on or failed to tolerate a range of first-line treatments including sunitinib, temsirolimus and cytokine-based immunotherapy.

Conclusion

Clinicians and patients now have multiple drugs available to them which are capable of doubling time to disease progression in RCC, and which also extend OS. The sequential, combination and dose-adjusted use of these drugs provide challenges to be tackled in future trials. New drugs targeting the VEGF ligand, tyrosine kinases and mTOR, as well as a myriad of other interesting targets are in trial and hold much promise. In the meantime, we must perfect the art of individual application of these new agents to patients in our clinics, revisiting our internal medicine roots and mastering supportive care, to maximize tolerability and benefit.

Conflict of interest statement

TBD, AG – none. DIQ has received honoraria from speakers' bureau and consulting as well as clinical trials support from Sanofi-Aventis, Millennium, Bayer Schering Healthcare, Onyx Pharmaceuticals, Pfizer, Genentech, Roche and Wyeth.

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