Systemic therapy for advanced renal cell carcinoma

James M.G. Larkin, Emma L.S. Kipps, Ceri J. Powell and Charles Swanton

Abstract: Renal cell carcinoma (RCC) accounts for approximately 3% of all cancers and is refractory to cytotoxic chemotherapy — immunotherapy has until recently been the standard of care for advanced disease. Randomised trials reported in the last 5 years have demonstrated that a number of agents including the monoclonal antibody, bevacizumab, and the kinase inhibitors — sorafenib sunitinib, temsirolimus and everolimus — are active in advanced RCC. Bevacizumab is directed against the vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, whilst sorafenib and sunitinib inhibit a number of targets including the VEGF and platelet-derived growth factor (PDGFR) receptor tyrosine kinases. Temsirolimus and everolimus inhibit the intracellular mammalian target of rapamycin (mTOR) kinase. Sunitinib and temsirolimus have demonstrated efficacy in comparison with immunotherapy in the first-line setting in patients with favourable and poor prognosis advanced disease respectively. In the second-line setting, everolimus has shown benefit over placebo in patients who progress following treatment with a VEGF receptor tyrosine kinase inhibitor and sorafenib has demonstrated efficacy in comparison with placebo in patients with immunotherapy-refractory disease. We review here recent clinical trial data and discuss future developments in the systemic treatment of RCC including combination and sequential therapy, adjuvant therapy, the role of biomarkers and the prospects for the development of rational mechanism-directed therapy in this disease.

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

Biology and pathology of renal cell carcinoma

Renal cell carcinoma (RCC) is a rare tumour with a rising incidence, currently accounting for approximately 3% of all cancers in the USA [Jemal *et al*. 2007]. Affected individuals may present with symptoms and signs of localised disease such as loin pain or haematuria but the diagnosis is increasingly made incidentally as a result of imaging performed for unrelated reasons. Up to a third of patients present with advanced disease and a third of patients treated surgically with curative intent relapse with advanced disease. Poor performance status, anaemia, high serum calcium and metastases in multiple organs are poor prognostic factors in advanced disease [Bukowski *et al*. 2004]. The average survival for patients with advanced RCC is approximately 12 months [Motzer *et al*. 2004] although the disease has a variable natural history: rapidly progressive disease is often seen but disease stability off treatment for prolonged periods of time and spontaneous regressions are both well documented

[Escudier *et al*. 2007a; Oliver *et al*. 1989]. The fact that disease stability is not uncommon means that single-arm therapeutic studies in advanced RCC need to be interpreted with caution as patient selection has a significant effect on outcome. Randomised studies are therefore necessary to draw firm conclusions.

RCC is histologically heterogeneous: approximately three quarters of tumours are of the clear cell subtype while papillary, chromophobe, medullary and collecting duct subtypes account for the remainder. These distinctions are important because clear cell histology is associated with dysfunction of the Von Hippel Lindau (VHL) gene in the majority of cases [Kaelin, 2007] but this association for other histological subtypes is less well understood. The product of the VHL gene (pVHL) is a component of an ubiquitin ligase complex that mediates the cellular response to hypoxia. In normoxic conditions pVHL is bound to hypoxia inducible factor-1α (HIF-1α)

Correspondence to:
James M.G. Larkin
Department of Medicine,
Royal Marsden Hospital,
London SW3 6JJ, UK
james.larkin@rmh.nhs.uk

Emma L.S. Kipps
Department of Medicine,
Royal Marsden Hospital,
London SW3 6JJ, UK

Ceri J. Powell
Department of Clinical
Oncology, Royal Marsden
Hospital, London
SW3 6JJ, UK

Charles Swanton
CR-UK Translational
Cancer Therapeutics
Laboratory, London
Research Institute,
44 Lincoln's Inn Fields,
London WC2A 3PX, UK

and HIF-2α which become ubiquitinated and tagged for degradation in the proteasome. In hypoxic conditions or in the absence of pVHL, HIF-1α accumulates, leading to the production of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor α (TGF-α) and vascular endothelial growth factor (VEGF). Activation of the mammalian target of rapamycin (mTOR) also leads to increased expression of HIF-1α [Brugarolas, 2007]. All these factors stimulate cellular proliferation and angiogenesis resulting in growth and progression of renal cell cancers and as such, constitute a possible therapeutic target in this subset of tumours.

Systemic treatment of advanced renal cell carcinoma

Introduction
Negligible response rates have been reported for the treatment of advanced RCC with chemotherapy [Yagoda and Bander, 1989] and hormone therapy [MRC RE01, 1999]. Higher response rates (10–20%) have been reported with subcutaneous interferon therapy in patients with good performance status [MRC RE01, 1999] and such treatment was regarded, until recently, as the standard of care for advanced disease. Since 2003, a number of novel agents have shown efficacy in the treatment of RCC and these data are reviewed below.

Immunotherapy
Immunotherapy is active in the treatment of both RCC and melanoma. Both diseases are relatively refractory to cytotoxic chemotherapy in comparison with other solid tumours but neither this resistance nor the sensitivity of immunotherapy is well understood. High dose intravenous interleukin-2 results in complete responses in approximately 5–10% of patients with advanced RCC. Disease control is prolonged in 70–80% of this subset [Rosenberg *et al.* 1998] but this treatment causes substantial toxicity and has not been evaluated against standard treatments in randomised trials. A survival benefit has been reported in the Medical Research Council (MRC) RE01 randomised trial for patients with advanced RCC treated with subcutaneous interferon at a dose of 10 MU three times a week in comparison with medroxyprogesterone acetate (MPA) 300 mg orally per day [MRC RE01, 1999]. Median overall survival for the interferon arm was 8.5 months in comparison with 6 months for the MPA arm. Given that the administration of immunotherapy

can be of clear benefit in a small subset but is associated with significant toxicity [Parton *et al.* 2006], there is a need to define the mechanism of action of such treatment and to identify possible markers of response in order to identify patients that may benefit [Atkins *et al.* 2005].

Monotherapy with novel agents
Six randomised studies of single agent therapy with novel agents in advanced RCC have been reported since 2003 (Table 1).

Bevacizumab Bevacizumab is a monoclonal antibody against VEGF, a key regulator of angiogenesis [Ferrara *et al.* 2003], a process necessary for the growth of solid tumours [Folkman, 1972]. Bevacizumab has shown activity in breast cancer [Miller *et al.* 2007], colorectal cancer [Hurwitz *et al.* 2004] and nonsmall cell lung cancer [Sandler *et al.* 2006] in combination with cytotoxic chemotherapy but little activity as a single agent has been reported. In contrast, in advanced RCC treatment with bevacizumab as a single agent led to an increase in time to disease progression in comparison with placebo in a three-arm randomised phase II study in the second-line setting reported in 2003 [Yang *et al.* 2003]. One hundred and sixteen patients were treated intravenously with placebo or bevacizumab at a dose of 3 mg/kg or 10 mg/kg every 2 weeks. Time to progression was significantly prolonged in the 'high dose' bevacizumab group in comparison with the placebo group (4.8 *versus* 2.5 months, hazard ratio = 2.55, $p < 0.001$) but the difference between 'low dose' bevacizumab and placebo was not statistically significant. The trial was stopped early on the basis of these data although only four responses to treatment occurred (response rate 10%, all in the 'high dose' arm) and no survival benefit was demonstrated. Bevacizumab was generally well tolerated: the main toxicities were asymptomatic proteinuria (25%) and hypertension (14%). This pivotal trial provided proof of the principle that VEGF is a clinically relevant therapeutic target in RCC.

Sunitinib Sunitinib is an orally administered inhibitor of the c-KIT, FLT-3, PDGFR and VEGFR2 tyrosine kinases that is active in the treatment of gastrointestinal stromal tumors (GISTs) after failure of imatinib therapy [Prenen *et al.* 2006]. A dose of 50 mg orally once a day for 4 weeks followed by a 2 week break was the recommended phase II dose based on two phase I studies [Faivre *et al.* 2006; O'Farrell *et al.* 2003].

Table 1. Randomised studies of novel single agent therapy in advanced renal cell carcinoma.

Agent(s)	Comparator(s)	Trial phase	Line of therapy	*n*	Reference
Bevacizumab (high dose)	1. Placebo 2. Bev (low dose)	II	2nd	116	[Yang *et al.* 2003]
Sorafenib	IFN-α	II	1st	189	[Escudier *et al.* 2009]
Sorafenib	Placebo	II	2nd/3rd	202	[Ratain *et al.* 2006]
Sorafenib	Placebo	III	2nd	903	[Escudier *et al.* 2007a]
Sunitinib	IFN-α	III	1st	750	[Motzer *et al.* 2007b]
Everolimus	Placebo	III	2nd	410	[Motzer *et al.* 2008a]

Bev, bevacizumab; IFN, interferon.

The results of a phase III trial comparing sunitinib with interferon-α in the first-line treatment of patients of performance status 0 or 1 with favourable and intermediate prognosis advanced clear cell renal carcinoma were reported early in 2007 [Motzer *et al.* 2007b]. The administration of sunitinib resulted in superior response rates (31% *versus* 6%, $p < 0.001$) and median progression-free survival (11 *versus* 5 months, hazard ratio (HR) 0.42, 95% confidence interval (CI) 0.32 to 0.54, $p < 0.001$). Adverse events were similar in both groups except that 5—10% of patients in the sunitinib group had grade three or four (i.e. severe or life-threatening) diarrhoea, hypertension or hand-foot syndrome ($p < 0.05$). Grade three or four neutropaenia and thrombocytopaenia were also more common in the sunitinib group, occurring in about 10% of patients ($p < 0.05$). Grade three or four fatigue was seen in 7% of patients in the sunitinib group and 12% in the interferon group ($p < 0.05$). Quality of life was also significantly better in the sunitinib than the interferon group ($p < 0.001$). An update on the survival analysis was more recently published in abstract form [Figlin *et al.* ASCO 2008, Abstract 5024]. Overall survival analysis showed a median survival of 26.4 months in the sunitinib group and 21.8 months in the interferon group (HR 0.821, $p = 0.051$). Additional data were presented indicating that many patients initially assigned to interferon either crossed over to sunitinib or, more likely, received subsequent sunitinib or other active treatments after progression. The median overall survival analysis in patients who did not receive any second-line therapy was 28.1 *versus* 14.1 months ($p = 0.0033$) in favour of sunitinib. As a result of these data, sunitinib is now considered standard first-line therapy for patients with favourable and intermediate prognosis advanced RCC.

There are also nonrandomised data from phase II trials to support the use of sunitinib as a second-line therapy in patients who are intolerant of or resistant to cytokine therapy. Rosenberg [Rosenberg *et al.*, ASCO 2007, Abstract 5095] reported the results of two phase II trials [Motzer *et al.* 2006a; 2006b]. Of 168 patients, 45% had an objective response with a median progression free survival of 8.4 months.

Sorafenib Sorafenib is orally administered and inhibits the BRAF and CRAF (Raf-1) nonreceptor serine threonine kinases, components of the RAF/MEK/ERK signalling cascade. Although often involved in tumour cell survival and proliferation, it is unknown if dysfunction of this pathway specifically is relevant to RCC. Sorafenib also inhibits the ^{V600E}BRAF mutant which is commonly present in melanoma [Davies *et al.* 2002] but is not reported in RCC [Nagy *et al.* 2003]. A number of receptor tyrosine kinases known to be involved in angiogenesis and tumourigenesis such as VEGFR2, Flt-3, c-KIT and PDGFR are also inhibited by sorafenib [Wilhelm *et al.* 2004] and sorafenib is the first-line treatment of choice in hepatocellular carcinoma on the basis of an overall survival benefit in a phase III study [Llovet *et al.* 2008].

Three randomised trials have evaluated sorafenib in the treatment of advanced RCC [Escudier *et al.* 2007a; Szczylik *et al.*, ASCO 2007, Abstract 5025; Ratain *et al.* 2006]. The phase II evaluation of sorafenib in advanced RCC was initially conducted in a randomised discontinuation trial (RDT) in the second-line setting [Ratain *et al.* 2006]. The RDT design distinguishes the efficacy of a study drug from slow disease growth [Stadler *et al.* 2005; Rosner *et al.* 2002]. All participants initially are treated with the study drug (stage 1) and those with stable disease after a predetermined interval undergo double-blinded randomisation between continued therapy and placebo (stage 2). Participants responding to

treatment at the end of stage 1 continue the study drug whilst treatment is discontinued in those with progressive disease. This study demonstrated a significant effect on PFS and an acceptable toxicity profile for sorafenib and provided the basis for phase III evaluation.

A phase III trial of sorafenib *versus* placebo in the second-line treatment of advanced RCC was reported early in 2007 [Escudier *et al.* 2007a]. The primary endpoint of the trial was overall survival; over 80% of patients had received prior cytokine therapy, all patients were of performance status 0 or 1 and all had clear cell histology. At a planned interim analysis, median progression-free survival was 5.5 months for sorafenib in comparison with 2.8 months for placebo (hazard ratio 0.44, $p < 0.01$) and crossover was permitted from placebo to sorafenib. There was no difference in overall survival between groups, possibly because crossover after the interim progression-free survival analysis confounded the overall survival analysis. The response rate to sorafenib was 10% in comparison with 2% to placebo ($p < 0.001$). Toxicities for sorafenib *versus* placebo were rash (34 *versus* 13%), diarrhoea (33 *versus* 10%), hand-foot skin reaction (27 *versus* 5%), fatigue (26 *versus* 23%), hypertension (11 *versus* 1%) and cardiac ischaemia (2.7 *versus* 0.4%). This trial shows that sorafenib is active in cytokine-refractory advanced RCC but associated with increased toxicity in comparison with placebo.

In the first-line setting, sorafenib has been compared with interferon-α (Table 1) [Escudier *et al.* 2009] in a randomised phase II trial. All patients had clear cell histology and were treated at 400 mg twice daily ($n = 97$) or interferon-α 9 MU subcutaneously three times a week ($n = 92$). Median progression-free survival (PFS) was similar in both groups (5.6 *versus* 5.7 months, hazard ratio 1.14, $p = 0.504$); sorafenib therapy is therefore not superior to interferon-α in the first line setting.

Temsirolimus mTOR is a serine/threonine protein kinase that regulates cell growth, growth proliferation and angiogenesis. Although mTOR lies downstream of Akt/PKB, inhibition of mTOR can lead to feedback activation of Akt/PKB, thus regulating apoptosis and proliferation in addition to its known ability to regulate cell growth. One of the three Akt/PKB isozymes, Akt1 is critical to the ability of endothelial cells and their precursors to respond to stimulation by VEGF [Weinberg, 2007]. Another potential rationale for mTOR inhibition in RCC is due to loss of the tumour suppressor protein, PTEN. Hara *et al.* found PTEN expression in RCC decreased and phosphorylated Akt expression increased significantly in comparison with that in the corresponding normal kidney tissue [Hara *et al.* 2005]. A decreased expression of PTEN may be an underlying mechanism for Akt activation, in part explaining why PTEN deficient cells are more sensitive to the activity of mTOR inhibitors through an increased phosphorylation state in the Akt pathway [Garcia and Danielpour, 2008].

Temsirolimus is an intravenously administered mTOR inhibitor which has shown activity in a phase II study in mantle cell lymphoma [Witzig *et al.* 2005]. Temsirolimus has been compared with interferon-α therapy and with the combination of both drugs as first-line therapy in a three arm randomised trial in patients with poor prognosis advanced RCC [Hudes *et al.* 2007]. Inclusion criteria for the study included at least three of the following poor-risk features: time from diagnosis to randomisation of less than a year, haemoglobin less than the lower limit of normal, corrected serum calcium $>10 \, \text{mg/dL}$ ($>2.50 \, \text{mmol/L}$), LDH > 1.5 times the upper limit of normal, Karnofsky performance status of 60–70 and multiple organ sites of metastases. Temsirolimus was administered at $25 \, \text{mg/m}^2$ once a week as a single agent and interferon-α at 18 MU three times a week as a single agent. In the combination arm, temsirolimus was given at $15 \, \text{mg/m}^2$ and interferon-α at 6 MU on the same schedules. Patients who received temsirolimus alone had longer overall survival (median 10.9 *versus* 7.3 months, HR for death 0.73, 95% CI 0.58 to 0.92, $p = 0.008$) and progression-free survival ($p < 0.001$) than did patients who received interferon-α alone. The outcomes in the combination therapy arm were similar to the interferon-α alone group. This may be a consequence of the lower dose of temsirolimus prescribed in the combination arm or perhaps because interferon has a lack of proven efficacy in this patient population. Temsirolimus as a single agent was generally better tolerated: for example, fatigue was the commonest grade three or four toxicity and was seen in 12% of patients on temsirolimus, 27% on interferon-α and 30% on the combination. Sixty nine per cent of patients on temsirolimus had at least

one grade three or four toxicity in comparison with 85% on interferon-*a* and 87% on the combination ($p < 0.001$ for both comparisons).

The greater efficacy of temsirolimus over both interferon-*a* and the combination of both drugs has defined temsirolimus as standard therapy in this group of patients. A potential criticism of this study is that single agent interferon-*a* therapy is not associated with a survival advantage in comparison with hormonal treatment in intermediate prognosis patients based on the results of the Percy Quattro study [Negrier *et al.* 2007]. It could be argued therefore that in the control arm of the temsirolimus study (interferon-*a*) does not constitute standard treatment in this group of patients. In the Percy Quattro study, 492 patients were treated in a 2×2 factorial design with medroxyprogesterone acetate 200 mg daily, subcutaneous interferon-*a* 9 MU three times a week, subcutaneous interleukin-2 9 MU daily, or a combination of both cytokines.

There are no randomised data to support the use of temsirolimus as second-line therapy. However, preliminary results from the Austrian Compassionate Use Program [Schmidinger *et al.*, 2008, ASCO 2008, Abstract 16125] of an open label phase II study of temsirolimus in 15 patients who progressed following prior therapy (including anti-VEGF) for advanced RCC have shown a response rate of 20%, a further 70% achieving disease stabilisation with a median progression free survival of 19 weeks. Although these results are from a small phase II trial, these data are comparable to that from the randomised phase III trial for everolimus [Motzer *et al.* 2008c], where a partial response rate of 1%, disease stabilisation of 63% and a median progression-free survival of 4 months was reported.

Everolimus Everolimus is an oral mTOR inhibitor. In a phase III randomised controlled trial, it has shown benefit over placebo in patients who progress following treatment with a VEGF receptor tyrosine kinase inhibitor; sunitinib (46%), sorafenib (28%) or both (24%) [Motzer *et al.* 2008b]. Four hundred and ten patients were randomly assigned in a two to one ratio to receive everolimus 10 mg or placebo in conjunction with best supportive care. Progression-free survival was 4.0 *versus* 1.9 months in favour of everolimus (HR 0.30 95% CI 0.22–0.40; $p < 0.001$). The trial was stopped early when the results of the second interim analysis indicated a significant difference in efficacy between arms in favour of everolimus. There was no significant difference between groups in terms of overall survival, which is probably due to confounding by crossover. Of the 98 patients in the placebo group who progressed as per investigator assessment, 79 crossed over to open-label everolimus. The most commonly reported toxicities were stomatitis (40%) and rash (25%) in the everolimus group with only stomatitis and pneumonitis seen at grade 3 intensity. This is the only published randomised controlled phase III trial investigating second line treatment in metastatic RCC following progression on anti-VEGF therapy.

Combination therapy

A large number of trials of combination therapy are currently underway and phase I/II combination data have already been reported for some agents [Escudier *et al.* 2007b; Motzer *et al.* 2007a; Ryan *et al.* 2007]. One prospective phase II trial, published in abstract form, combined sorafenib with interferon in two different schedules (9 MU three times a week or 3 MU five times a week) as first line treatment of metastatic RCC [Bracarda *et al.*, ACSO 2007, Abstract 5100]. An overall response rate of 25.4% and a tumour control rate (partial response + stable disease) of 66.7% were reported. Grade three and four toxicities were present in more than 5% of patients and equally divided between the regimes other than fatigue and skin rash which affected 19% and 8% of patients respectively who prescribed the higher dose of interferon. However, combination of immunotherapy with novel agents has generally resulted in increased toxicity and a subsequent reduction in dose. Interferon-*a* given in combination with both VEGFR TKI inhibitors [Kondagunta *et al.*, ASCO 2007, Abstract 5101] and mTOR inhibitors [Motzer *et al.* 2007a] have resulted in toxicity without reports of increased efficacy. For example, one phase II study of sorafenib and interferon-*a* reported a 33% response rate (13/40) but 65% of patients required a dose reduction [Gollob *et al.* 2007].

Significant toxicity has also been reported following simultaneous inhibition of VEGF and mTOR pathways. Both sorafenib [Patnaik *et al.*, ASCO 2007, Abstract 3512] and sunitinib [Fischer *et al.*, ASCO 2008, Abstract 16020] in combination with temsirolimus have shown significant toxicity. Interestingly, phase II data have shown bevacizumab in combination with both

everolimus [Whorf *et al.*, ASCO 2008, Abstract 5010] and temsirolimus [Merchan *et al.*, ASCO 2007, Abstract 5034] to be tolerable at full doses of both agents, together with promising evidence of efficacy.

To date only four randomised studies of combination therapy have been published in peer-reviewed journals (Table 2).

Bevacizumab and interferon Escudier *et al.* and Rini *et al.* enrolled 649 and 732 previously untreated patients respectively, to two phase III studies comparing the combination of bevacizumab 10 mg/kg given every 2 weeks and interferon-*α* 9 MU three times per week with interferon-*α* alone. The combination of agents significantly increased progression-free survival (10.2 *versus* 5.4 months, hazard ratio 0.63, $p < 0.0001$ [Escudier *et al.* 2008], 8.5 months *versus* 5.2 months, hazard ratio 0.71, $p < 0.0001$ [Rini *et al.* 2008c]. In the AVOREN study [Escudier *et al.* 2008], patients aged over 65 years were reported to benefit to a similar extent from combination therapy compared with patients less than 65 years of age [Bajetta *et al.*, ASCO 2008, Abstract 5095] and the incidence of grade 1–5 adverse events was similar between age groups. Although overall toxicity was not severe, it was greater for combination treatment, including significantly more grade three hypertension (9 *versus* 0%), anorexia (17 *versus* 8%), fatigue (35 *versus* 28%), and proteinuria (13 *versus* 0%) [Rini *et al.* 2008a]. Escudier *et al.* also reported combination treatment to be well tolerated, with fatigue the most commonly reported grade three or greater adverse event (12% patients in the combination *versus* 8% in the interferon group). These are the only published data demonstrating synergy for combination therapy in the treatment of advanced RCC;

of note, both agents are active as single agents in patients with good performance status and advanced RCC. Although sunitib has never been directly compared to interferon and bevacizumab in combination, the latter may be the preferred choice for patients with preexisting skin or bowel conditions in whom the anticipated toxicity with sunitinib is best avoided.

Bevacizumab and erlotinib The epidermal growth factor receptor (EGFR) is over-expressed in approximately two thirds of RCCs [Uhlman *et al.* 1995] and three phase II studies of the EGFR tyrosine kinase inhibitor gefitinib as a single agent in advanced RCC have been published [Jermann *et al.* 2006; Dawson *et al.* 2004; Drucker *et al.* 2003]. Sixty seven patients were treated in these studies without evidence of efficacy. Considerable interest therefore was generated by the report of possible synergy between the EGFR tyrosine kinase inhibitor (TKI) erlotinib and bevacizumab [Hainsworth *et al.* 2005]. By simultaneously targeting different pathways ('horizontal blockade'), 63 patients with advanced clear cell renal carcinoma were treated with the combination of bevacizumab 10 mg/kg intravenously every 2 weeks and erlotinib 150 mg orally daily in a phase II trial. Fifteen patients (25%) had objective responses (14 partial responses and one complete response). Thirty six patients (61%) had stable disease and 13 of these patients had minor objective responses (10–30% decrease in tumour size). The median progression-free survival was 11 months and median survival had not been reached at the time that the study was reported. A randomised phase II trial of 103 patients comparing bevacizumab with the combination of bevacizumab and erlotinib [Bukowski *et al.* 2007] did not report any difference in response rate or survival between the two arms, thereby

Table 2. Randomised studies of single agent versus novel combination therapies in advanced renal cell carcinoma.

Agent(s)	Comparator(s)	Trial phase	Line of therapy	*n*	Reference
Bevacizumab + erlotinib	Bevacizumab	II	1st	104	[Bukowski *et al.* 2007; Escudier *et al.* 2007b]
Temsirolimus + IFN-*α*	1. IFN-*α* 2. Temsirolimus	III	1st	626	[Hudes *et al.* 2007]
Bevacizumab + IFN-*α*	IFN-*α*	III	1st	649	[Escudier *et al.* 2008]
Bevacizumab + IFN-*α*	IFN-*α*	III	1st	732	[Rini *et al.* 2008b]

IFN, interferon.

demonstrating the importance of randomised trial data in this disease.

Areas of uncertainty

Research into the molecular and genetic aspects of angiogenesis and tumourigenesis in RCC is increasing. However, there remain large areas of uncertainty. Until the way in which newer targeted agents affect the biology of RCC is understood, the role of novel agents in the adjuvant and neo-adjuvant setting remains uncertain. It is also unclear as to how patients should be selected for therapy and how patients with nonclear cell histology should be treated.

The availability of anti-angiogenic drugs has increased dramatically over recent years. As a consequence, sequential anti-angiogenic therapy in some parts of the world has become common place. A biological rationale exists for using VEGF as a therapeutic target. There are multiple pathways which respond to hypoxia [Mizukami *et al.* 2007] and it is therefore reasonable to study the potential clinical benefit of sequential treatment with anti-angiogenic drugs following development of drug resistance. As a consequence, new drug targets may be discovered if specific mutations were found to correlate with resistance [Brugarolas, 2007]. However, mutations in the normal vasculature may not be responsible for the resistance observed. It is possible that the mechanism of resistance may be a direct consequence of the primary tumour secreting neo-angiogenic factors and therefore that novel targeted therapies may be acting in a tumour autonomousmanner. Data regarding resistance of targeted agents and sequential anti-angiogenic treatment, along with other key questions in the management of advanced RCC are discussed below.

Is there a role for novel agents in the adjuvant or preoperative setting?

Although immunotherapy has proven efficacy in advanced disease, no benefit has been shown in the adjuvant setting [Clark *et al.* 2003; Messing *et al.* 2003; Pizzocaro *et al.* 2001]; in fact, a reduction in overall survival has been reported with immunotherapy in comparison with placebo [Atzpodien *et al.* 2005]. Three adjuvant studies of kinase inhibitor therapy in RCC are recruiting: the ASSURE (adjuvant sorafenib or sunitinib for unfavourable RCC) study is a three arm randomised trial comparing 1 year of adjuvant therapy with sorafenib *versus* sunitinib *versus* placebo in patients with resected high risk disease. The Medical Research Council RE05/SORCE study is a three-arm randomised trial comparing sorafenib for 1 year *versus* sorafenib for 3 years *versus* placebo in patients with intermediate or high risk resected disease. The S-TRAC trial is recruiting to compare the disease free survival time and safety of sunitinib with placebo for 1 year, in the adjuvant treatment of patients at high risk of recurrent kidney cancer after surgery.

Two randomised trials have reported that debulking nephrectomy results in an overall survival benefit in patients with advanced RCC and good performance status when subcutaneous interferon is given postoperatively, in comparison with the administration of interferon alone [Flanigan *et al.* 2004; Flanigan *et al.* 2001; Mickisch *et al.* 2001]. As a consequence of these data, a large number of patients with metastatic RCC undergo nephrectomy and an opportunity exists therefore to evaluate novel systemic agents in the preoperative setting. In a small trial recently published [Thomas *et al.* 2009], four out of 19 patients with inoperable RCC successfully underwent a nephrectomy following preoperative sunitinib therapy. Further research in this area has two potential merits: first, in the event that tumour shrinkage occurs, surgery may be technically easier and second, biomarkers of response and resistance to treatment can be evaluated by comparing a pretreatment biopsy with the nephrectomy specimen. Changes in biomarkers can then be correlated with clinical endpoints.

How should patients be selected for therapy?

Three classes of agent are active in RCC: immunotherapy, anti-VEGF/anti-PDGF therapy and anti-mTOR therapy. Performance status, histology and the presence of poor prognostic factors are the only markers currently used to select patients with advanced RCC for different therapies. Almost all patients enrolled in the trials discussed above were of good performance status and had clear cell histology; these data cannot be extrapolated to patients with poor performance status or nonclear cell histology and the treatment of the latter group is discussed in the section below. Based on the trial data discussed already, temsirolimus is the first-line treatment of choice in patients with clear cell carcinoma and poor prognostic factors and sunitinib the treatment of choice in patients with favourable or intermediate prognosis.

Currently there are no other factors in RCC that can be used to select patients for particular treatments although carbonic anhydrase IX expression has been reported to predict out to interleukin-2 therapy [Atkins *et al.* 2005]. Importantly, there are no known predictive markers for benefit from anti-angiogenic therapy in RCC or in other tumour types that such treatment is active [Duda *et al.* 2007].

How should patients with nonclear cell histology be treated?

A case series of patients with advanced papillary ($n = 41$) and chromophobe RCC ($n = 12$) treated with sunitinib or sorafenib has been reported [Choueiri *et al.* 2008]. The response rate for chromophobe histology was 25% ($n = 3$, two to sorafenib and one to sunitinib) and 5% ($n = 2$, both to sunitinib) for papillary histology. The median progression-free survival and overall survival for the entire series was 8.6 months and 19.6 months respectively. Patients with papillary histology treated with sunitinib had a progression-free survival of 11.9 months in comparison with 5.1 months for sorafenib ($p < 0.001$). Prospective trial data are awaited to clarify the role of therapy with novel agents in nonclear cell RCC.

Patients who have metastatic RCC and sarcomatoid differentiation (between 3 and 90%) can demonstrate objective responses and tumor shrinkage to VEGF-targeted therapy. When adjusted for stage, necrosis, and tumor size, patients with tumors with sarcomatoid differentiation have a worse prognosis [de Peralta-Venturina *et al.* 2001]. Golshayan *et al.* retrospectively identified patients with metastatic RCC with sarcomatoid features in the primary tumour who were treated with sunitinib (49%), sorafenib (28%), bevacizumab (19%), or sunitinib plus bevacizumab (5%) [Golshayan *et al.* 2009]. Twenty-one patients of the 43 patients identified had stable disease whilst 33% had disease progression as the best response to treatment. Interestingly, a partial response had been seen in eight patients all of whom had underlying clear-cell histology and less than 20% sarcomatoid elements. At the time of analysis, 39 (91%) of 43 patients had progressed, and 25 (58%) of 43 had died. The median progression free survival was 5.3 months, and median overall survival was 11.8 months.

What is the role of sequential use of anti-angiogenic drugs?

One strategy for overcoming acquired resistance to one anti-angiogenic therapy has already been discussed, as everolimus, by blocking mTOR, has been proven to provide clinical benefit following progression on either sorafenib or sunitinib.

Retrospective data recently published [Dudek *et al.*, 2009] and presented in abstract form [Sablin *et al.*, ASCO 2007, Abstract 5038], support the sequential use of sorafenib and sunitinib suggesting a lack of crossresistance. Dudek *et al.* performed a retrospective study to compare the efficacy of the drugs measured by time-to-progression of sequential therapy with sorafenib followed by sunitinib, versus sunitinib followed by sorafenib. Twenty-nine patients received sorafenib followed by sunitinib (group A) and 20 patients received sunitinib followed by sorafenib (group B). The median duration of stable disease for groups A and B was 20 and 9.5 weeks respectively. The median time from starting first TKI to disease progression after second TKI in groups A and B was 78 and 37 weeks respectively with the median overall survival calculated as 102 and 45 weeks in Groups A and B respectively.

Retrospective data have recently been published confirming sorafenib and sunitinib appear to have significant activity in the setting of disease progression after previous anti-angiogenic therapy [Tamaskar *et al.* 2008]. Results from a case series of 30 patients treated with sunitinib ($n = 16$) or sorafenib ($n = 14$) that had been previously treated with other anti-angiogenic therapy were reported. Previous anti-angiogenic treatments included axitinib (AG-013736), bevacizumab, lenalidomide, sorafenib, sunitinib, thalidomide and volociximab (an inhibitor of the $\alpha 5 \beta 1$ integrin). The majority of patients had some response to treatment (13/16 on sunitinib and 10/14 on sorafenib). Partial responses were seen in 9/13 on sunitinib and 1/14 patients on sorafenib with an overall median time-to-progression of 10.4 months.

Data from open-label, nonrandomised trials assessing the safety and efficacy of sorafenib [Drabkin *et al.*, ASCO 2007, Abstract 5041] and sunitinib [Rini *et al.* 2008d] in patients with bevacizumab refractory disease, have been published. Seventy-seven per cent (152/185) of patients who received sorafenib in an expanded access programme had stable disease and 2.5%

(5/195) had a confirmed partial response [Drabkin *et al.*, ASCO 2007, Abstract 5041]. Rini *et al.* conducted a single-agent, nonrandomised prospective study by enrolling 61 patients to be treated with sunitinib, reporting a response rate of 23%. The median progression-free survival and duration of response was 30.4 weeks and 44.1 weeks, respectively.

Axitinib is an inhibitor of VEGFRs 1, 2 and 3 and has demonstrated activity in the treatment of cytokine-refractory advanced RCC in a phase II study [Rixe *et al.* 2007]. Interestingly, Tammela *et al.* reported that stimulation of VEGFR-3 augmented VEGF-induced angiogenesis and sustained angiogenesis even in the presence of VEGFR-2 inhibition, suggesting that VEGFR-3 may drive angiogenesis even in conditions of therapeutic targeting of VEGFR-2 [Tammela *et al.* 2008]. Recent phase II data presented in abstract form also demonstrate activity of axitinib in sorafenib pretreated RCC [Rini *et al.*, ASCO 2007, Abstract 5032]. All patients in this study had received prior sorafenib and 9 had also received prior sunitinib. Partial responses were observed in 6/42 evaluable patients (14%) and stable disease was documented in 15 patients (36%); the median progression-free survival had not been reached at a median follow-up of 5.3 months. Of note, no responses to axitinib were reported in patients previously treated with sunitinib.

There is a lack of data on the sequential use of mTOR inhibitors. From clinical studies, it is clear that the disease biology of patients with a high risk RCC is primarily driven by the mTOR pathway. The changes in the tumour biology, once resistance to mTOR inhibition is established, are unknown but it is likely that alternative pathways must be targeted. Assessing sequential mTOR inhibition is also problematic given the poor prognostic risk factors of the subpopulation of interest.

There are significant data to support the use of sequential anti-angiogenic drugs in the treatment of RCC. Targeting VEGFR-3 may provide additional efficacy for anti-angiogenic therapies, especially towards vessels that are resistant to VEGF or VEGFR-2 inhibitors [Tammela *et al.* 2008]. Successful prevention of tumour progression may therefore require the inhibition of multiple angiogenic targets. Given the toxicities associated with anti-angiogenic therapies, sequential use may be a more favorable approach than combination treatment.

There is currently a paucity of surrogate markers for the sensitivity or resistance to anti-angiogenic drugs. The biological mechanisms by which resistance develops, lacks understanding and as a result, sequential therapy cannot be fully exploited. Harnessing this information with the use of biomarkers, would result in treatment being tailored more appropriately to the individual.

Conclusions

The treatment of RCC is now centering on the use of agents which block the VEGF pathway or the mTOR pathway. Randomised trials have demonstrated that bevacizumab, sorafenib, sunitinib, everolimus and temsirolimus are active as single agents in advanced RCC. All of these trials have used interferon-α or placebo as the control arm and these treatments have not been compared with each other in randomised trials. Sunitinib is the first-line treatment of choice in patients with good prognostic factors and temsirolimus the treatment of choice in patients with poor prognostic factors. The activity of sunitinib in poor prognosis disease and of temsirolimus in good prognosis disease has not been evaluated prospectively. The combination of interferon-α and bevacizumab is more active in the first-line treatment of RCC than interferon-α but no other combination of agents has demonstrated additive activity to date. In the second-line setting everolimus has shown benefit over placebo in patients who progress following treatment with a VEGF receptor tyrosine kinase inhibitor.

The role of novel agents in the adjuvant setting and the optimal therapy of nonclear cell histology remain under investigation. In addition, sequential anti-angiogenic therapy remains an unexploited niche in the treatment of RCC. As a group of drugs, there is overwhelming evidence to support their efficacy, and there is a theoretical rationale for sequential use. However, what remain uncertain are the molecular mechanisms, in the differing subtypes of carcinoma, which render the patient resistant to one treatment whilst remaining sensitive to the next. There is a pressing need for biomarkers in order to select patients for a particular therapy; the administration of systemic treatment prior to debulking nephrectomy in patients with metastatic disease with molecular analysis of tumour

tissue before and on treatment provides a valuable opportunity in this regard. This approach also has the potential to provide further insights into the biology of RCC and into the mechanism of action of the novel agents that have entered clinical use in the last 5 years.

Conflict of interest statement
None declared.

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