Treatment options in renal cell carcinoma: past, present and future

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Cytokine therapies have been the standard of care in metastatic renal cell carcinoma (RCC). However, these agents only provide clinical benefit to a small subset of patients and are associated with significant toxicity. A better understanding of the molecular biology of RCC has identified the vascular endothelial growth factor (VEGF) and platelet-derived growth factor signalling pathways as rational targets for anticancer therapy. The multitargeted receptor tyrosine kinase inhibitors sunitinib and sorafenib have both demonstrated improved efficacy as second-line therapy in patients with RCC. Sunitinib has also been shown to be effective in the first-line setting, and has recently received European Union approval as first-line treatment for advanced and/or metastatic RCC. There is also recent evidence that temsirolimus (an inhibitor of the mammalian target of rapamycin) and bevacizumab (a mAb targeted against VEGF) may provide benefits in the first-line treatment setting. These results confirm that inhibiting these tumour targets is a feasible approach to treatment and provides a more positive outlook for the future management of metastatic RCC.

Key words: receptor tyrosine kinase inhibitor, renal cell carcinoma, sorafenib, sunitinib, temsirolimus

introduction

Renal cell carcinoma (RCC) accounts for ~2% of all cancers globally, with the highest rates observed in North America, Australia and Europe. In Europe, there are ~40 000 new cases diagnosed each year, leading to an estimated 20 000 deaths [1]. For patients with clinically localized disease, the 5-year relative survival rates range from 90.4% for patients with organ-confined disease to 61.7% for patients with regional spread [2]. However, because there are no standard screening tests for RCC, up to one-third of patients have metastatic disease at diagnosis [3, 4]. In patients with distant metastases, the 5-year survival is 9.5% [2]. For early stage, localized RCC, surgery is the primary approach; however, surgical resection of locally advanced disease is associated with a high recurrence [5]. Furthermore, in metastatic RCC, surgery does not usually alter disease progression [6]. Metastatic RCC is generally resistant to standard chemotherapy, radiotherapy and hormonal therapy. Objective response rates (ORR) of <10% have been reported with frequently used chemotherapeutic agents (gemcitabine, fluorouracil, capcitabin, vinblastine) [7] and combination treatment with gemcitabine plus capcitabin in 60 patients with metastatic RCC was associated with an ORR of 15% [8].

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cytokine therapy

Cytokine therapy with interleukin-2 (IL-2) or interferon-alpha (IFN-α) has until recently been considered the standard of care for the first-line treatment of metastatic RCC. However, only 10%–20% of patients experience objective disease response [9–11] and both IL-2 and IFN-α are associated with significant toxicity. A survival time of >5 years was observed in only 4.5% of patients (n = 30) among a cohort of 670 patients with advanced RCC treated with cytokine therapy [12]. Of these patients, only 1.8% was disease free [12]. In the French PERCY Quatro study, cytokine therapy did not offer a survival benefit in patients with metastatic RCC of intermediate prognosis, and was also associated with a high risk of toxicity [13]. For example, there were 78, 143 and 209 grade 3/4 toxic events in the IFN-α (n = 122), IL-2 (n = 125) or IFN-α plus IL-2 (n = 122) groups, respectively. In the second-line treatment setting (patients who had failed one cytokine therapy), treatment with another cytokine (e.g. interferon following high-dose IL-2 failure) is associated with even worse results and objective responses seen in <5% of patients [14].

rationale for multitargeted therapies

Approximately 80% of kidney tumours demonstrate clear-cell carcinoma histology [4, 15], which is associated with mutational inactivation of the von Hippel–Lindau (VHL) tumour suppressor gene. Loss of VHL gene function leads to overexpression of a number of hypoxia-responsive proteins,
such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which promote tumour growth and angiogenesis [16]. Consequently, inhibiting the VEGF and PDGF signalling pathways are rational targets for antiangiogenic therapy, particularly in clear-cell RCC. By inhibiting VEGF and PDGF receptors, signalling pathways involved in tumour growth and survival are disrupted and tumour progression slowed [17, 18]. Since several of these growth factor pathways involve a family of related receptor tyrosine kinases (RTKs) and ligands with overlapping biologic function, focusing on multiple targets is an attractive option. A number of multitargeted anticancer therapies have been developed for the treatment of RCC, including the small-molecule RTK inhibitors (e.g. sunitinib and sorafenib). These agents have demonstrated benefit as first- and/or second-line therapy in metastatic RCC. The remainder of this review discusses the recent results of targeted therapy in the treatment of RCC, focusing on studies with sunitinib, sorafenib, the mammalian target of rapamycin (mTOR) inhibitor temsirolimus and bevacizumab. The future potential of these agents in the adjuvant treatment of RCC and ongoing studies will also be outlined.

**sunitinib malate (Sutent®)**

**phase II studies (second-line)**

Sunitinib is an oral, multitargeted RTK inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, as well as other RTKs including stem cell factor receptor (KIT), glial cell line-derived neurotrophic factor [Rearranged during Transfection (RET)] and FMS-like receptor tyrosine kinase (Flt3) [19–22]. Sunitinib was approved in 2006 by the European Medicines Agency (EMEA) for use in advanced and/or metastatic RCC and by the United States Food and Drug Administration (FDA) for the treatment of advanced RCC. At the same time, sunitinib was approved by the EMEA for use in unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance and by the United States Food and Drug Administration (FDA) for the treatment of GIST after disease progression on or intolerance to imatinib mesylate treatment (See Judson et al. in this supplement).

The efficacy of sunitinib has been demonstrated in two independent, single-arm, multicentre, phase II studies (trial 1: n = 63; trial 2: n = 106) in patients with cytokine-refractory metastatic RCC [23, 24]. Sunitinib was administered at a dose of 50 mg/day on a 4 weeks on/2 weeks off schedule. Dose reductions to 37.5 mg/day and then to 25 mg/day were permitted based on individual patient tolerability. Patients continued on sunitinib unless there was disease progression or treatment was not tolerated. The primary end point for both studies was the ORR which was assessed every one to two cycles using the Response Evaluation Criteria in Solid Tumours [25]. The ORR was defined as the proportion of patients with a confirmed complete response (CR) or a partial response (PR). Secondary end points included overall survival (OS) and time to tumour progression (TTP) in the first study and progression-free survival (PFS) in the second study. Similar trial designs permitted a subsequent pooled analysis of the data [24].

### Table 1. Sunitinib response rates (investigator assessed) in two phase II trials and a pooled analysis in cytokine-refractory metastatic renal cell carcinoma [24]

<table>
<thead>
<tr>
<th>Response</th>
<th>Trial 1 (N = 63)</th>
<th>Trial 2 (N = 105)</th>
<th>Pooled analysis (N = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response, n (%)</td>
<td>25 (40)</td>
<td>46 (44)</td>
<td>71 (42)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>PR</td>
<td>25 (40)</td>
<td>45 (43)</td>
<td>70 (42)</td>
</tr>
<tr>
<td>SD ≥ 5 months, n (%)</td>
<td>17 (27)</td>
<td>23 (22)</td>
<td>40 (24)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.7 (5.5–10.7)</td>
<td>8.1 (5.5–10.4)</td>
<td>8.2 (7.8–10.4)</td>
</tr>
</tbody>
</table>

*One patient was excluded from the efficacy analysis after a repeat biopsy showed a diagnosis of a different type of cancer.

*Time to tumor progression [23].

CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; CI, confidence interval.

The pooled results showed that 42% of patients were responders and 24% had stable disease (SD) for at least 3 months (Table 1). This response rate is greater than has been previously reported with conventional second-line cytokine therapy (<50%) [14, 26].

Median PFS for all patients was 8.2 months [95% confidence interval (CI): 7.8 to 10.4]. The median PFS was 14.8 months for patients who achieved a CR or PR, and 7.9 months for those with SD (≥3 months).

Treatment with sunitinib was generally well tolerated. The tolerability profile of sunitinib was similar across the trials. The majority of adverse events reported were manageable with temporary delays, dose reduction and/or standard medical interventions. Dose reductions were required by approximately one-third and one-quarter of patients in trials 1 and 2, respectively. The most commonly reported grade 3, non-haematological treatment-related adverse events included fatigue (11% in both trials) and hand-foot syndrome (7% in trial 2). No non-haematological adverse events were experienced at grade 4 severity.

**phase III study (first-line)**

On the basis of the favourable phase II efficacy and safety data, a multicentre, randomized phase III study compared sunitinib with IFN-α as first-line therapy in metastatic RCC [27]. A total of 750 patients were randomly assigned to receive repeated 6-week cycles of sunitinib (n = 375; 50 mg/day for 4 weeks followed by 2 weeks off treatment) or IFN-α by s.c. injection three times weekly on non-consecutive days (n = 375; 3 MU per dose during the first week, 6 MU per dose during the second week and 9 MU per dose thereafter). Baseline characteristics were well balanced between groups; the pooled median age was 60 years and 90% of patients had prior nephrectomy. The primary end point was PFS; secondary end points included ORR, OS and safety. Results are available from a pre-planned interim analysis. Median PFS, as assessed by third-party independent review, was significantly longer with sunitinib (11 months; 95% CI: 10 to 12) than IFN-α (5 months; 95% CI: 4 to 6; P < 0.001). Significantly more patients on sunitinib achieved an ORR compared with IFN-α (investigator assessment, 37% versus 9%; P < 0.001; independent central review, 31% versus...
First-line sunitinib was well tolerated. The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with IFN-α (12% versus 7%; \( P < 0.05 \)), whereas grade 3 diarrhoea was more frequent in the sunitinib group (5% versus 0%; \( P < 0.05 \)). In the sunitinib group, 30 (8%) patients withdrew from the study due to an adverse event versus 47 (13%) in the IFN-α group [27]. Sunitinib has recently received European Union approval as first-line treatment for advanced and/or metastatic RCC.

other studies with sunitinib in RCC

Additional phase II studies are ongoing to assess the efficacy of sunitinib in RCC. These studies are evaluating sunitinib administered at different dosing schedules, in different patient populations and in combination with other targeted agents (i.e. gefitinib) to provide patients with tailored treatment and thus potentially optimal therapy. For example, an ongoing expanded access study is investigating sunitinib in patients who are ineligible for participation in any ongoing phase I, II or III clinical trials but who may derive clinical benefit from sunitinib as assessed by the investigating physician [28]. For this study, sunitinib was made available to expand access to the drug and also to allow patients to be treated in countries where regulatory approval is yet to be granted. This study continues to assess the safety and efficacy of sunitinib 50 mg/day administered on the 4/2 schedule with dose reduction permitted for toxicity. Preliminary data indicate that sunitinib is generally well tolerated. At the time of writing, \( > 5000 \) patients had received at least one dose of sunitinib.

In another study, the effects of continuous once-daily administration of sunitinib [37.5 mg/day administered in the morning (AM) or evening (PM)] is being investigated in 107 patients with cytokine-resistant metastatic RCC [29]. Preliminary efficacy results from 62 patients showed tumour shrinkage in nine patients, with a confirmed PR in three patients (ORR = 5%). The median time to achieve an initial PR was 3 months (three cycles). Forty-three patients (69%) had SD for a median of 3 months. These preliminary data indicate that sunitinib is generally well tolerated, and that the safety profile is comparable between AM and PM dosing and also with the current recommended regimen of sunitinib (50 mg/day on a 4 weeks on, 2 weeks off schedule). During the 31st European Society of Medical Oncology congress, updated results were presented and the PR rate was 14.6%.

It is thought that RCC tumour resistance to bevacizumab may be partly driven by pathways that are sensitive to inhibition by sunitinib. To test this hypothesis, a phase II, single-arm, multicentre study is under way to evaluate the activity of sunitinib (50 mg daily, 4 weeks on/2 weeks off) in patients with bevacizumab-refractory metastatic RCC [30]. Of the 55 patients who were assessable for response, 48 (87%) had some degree of tumour shrinkage, including six patients (11%) with a PR.

**sorafenib tosylate (Nexavar®)**

Sorafenib is an oral, multitargeted kinase inhibitor. The molecular targets of sorafenib include the tyrosine kinases VEGFR-2 and-3, PDGFR-β, FLT3, KIT and RET, and the serine/threonine Raf kinases, B-Raf and Raf-1/C-Raf. Sorafenib received approval from EMEA in July 2006 for the treatment of advanced RCC after failure of prior cytokine therapy or for patients who would be unsuitable for such therapy. FDA approval was granted in December 2005 for the treatment of patients with advanced RCC.

The efficacy of sorafenib in the second-line setting was initially seen in a phase II randomized discontinuation trial [31]. The trial included a lead-in stage during which all patients received sorafenib for 12 weeks. Patients with SD were then randomized to either continued sorafenib or placebo (patients with \( ≥ 25\% \) tumour shrinkage continued on open-label sorafenib). The primary end point was the percent of randomized patients remaining progression free at 24 weeks; significantly more RCC patients on sorafenib were progression free than patients on placebo (50% versus 18%; \( P < 0.0077 \)). Median PFS after randomization was also longer in the sorafenib group (24 weeks; \( n = 32 \)) than the placebo group (6 weeks; \( n = 33 \); \( P = 0.0087 \)). Prior to randomization (after 12 weeks of therapy), 73 patients (36%) had tumour shrinkage \( ≥ 25\% \), 69 patients (34%) had disease stabilization (tumour size within 25% of baseline) and 51 patients (25%) had progressive disease (225% tumour growth or other evidence of disease progression at or before week 12) [31]. Investigator-assessed ORR by modified World Health Organization criteria was 11% (\( N = 202 \)) and for 32 patients who received sorafenib as first-line treatment, the ORR was 19% (Negrier, personal communication).

Results from the randomized discontinuation study then led to an international phase III randomized controlled study of sorafenib versus placebo in patients with previously treated RCC. In this 'Treatment Approaches in Renal cell cancer Global Evaluation Trial', patients with unresectable or metastatic RCC were randomized to sorafenib 400 mg twice daily or placebo [32]. Investigator-assessed median PFS was twice as long for the sorafenib group compared with the placebo group (5.9 months versus 2.8 months; hazard ratio (HR) = 0.44; \( P < 0.001 \)). After the first interim analysis of OS, which showed that sorafenib reduced the risk of death as compared with placebo (HR = 0.72; \( P = 0.02 \) (this did not reach the level of significance specified for this interim analysis according to the O’Brien-Fleming Stopping Boundary of \( P = 0.0005 \)), patients were allowed to crossover from placebo to sorafenib. Of 451 patients receiving sorafenib and who were assessable for investigator-assessed response, 10% achieved a PR, and 74% had SD compared with 2% and 53%, respectively, in the placebo-treated arm (\( n = 452 \)) [32]. AEs were similar in phase II and III studies. The most commonly reported grade 3/4 AEs included dermatologic events (including hand–foot syndrome), fatigue and hypertension. In the phase III study, dose discontinuations, reductions and interruptions due to AEs occurred in 10%, 13% and 21% of patients in the sorafenib arm, respectively, compared with 8%, 3% (\( P < 0.001 \)) and 6% (\( P < 0.001 \)) of patients in the placebo arm [32]. AEs generally occurred at a greater incidence in sorafenib-treated patients than in placebo-treated patients and the most common AEs (of any grade) were as follows: diarrhoea (43% versus 13%); rash or
desquamation (40% versus 16%); fatigue (37% versus 28%) and hand–foot skin reactions (30% versus 7%) [32].

**Other studies with sorafenib in RCC**

The efficacy of sorafenib in combination with bevacizumab is under investigation in a phase I/II study in patients with previously treated metastatic RCC [33]. Preliminary results indicate that the combination is associated with antitumour activity; however, sorafenib toxic effects such as hand–foot syndrome are increased with the combination.

An ongoing randomized phase II study is also investigating the efficacy of sorafenib compared with IFN-α in the first-line setting [34]. Patients are being randomly assigned to sorafenib 400 mg twice daily or IFN-α 9 MU three times per week. On progression, the dose of sorafenib can be increased to 600 mg twice daily or patients can crossover from IFN-α to sorafenib 400 mg twice daily. The primary end point is PFS. Preliminary data (N = 188) indicate that sorafenib is generally well tolerated as first-line therapy. The most common treatment-related adverse events include diarrhoea (sorafenib 25% versus IFN-α 6%), fatigue (14% versus 21%), fever (2% versus 19%) and hypertension (13% versus 0%). In a filing to the SEC in the United States, progression in 125 patients to sorafenib 250 mg/week as a 30-min i.v. infusion [38]. Modest single-agent antitumour activity was demonstrated; the ORR was 25% versus IFN-α 17%; CR = 4% has been observed [37]. In the second study, of 53 assessable patients, the ORR was 19% (PR = 17%; CR = 2%) [36]. Despite these benefits, the addition of IFN-α appeared to increase the incidence of drug-related toxicity.

### Temsirolimus (Torsel®)

Temsirolimus is a kinase inhibitor of mTOR. Stimulation of mTOR results in the expression of several proteins involved in cell cycle progression, and also controls protein synthesis in response to oxygen starvation (including synthesis of HIF-1α in RCC cells) [37]. Application for approval was submitted to the European Commission and FDA in 2006. Temsirolimus received a positive opinion from EMEA and was granted accelerated review by the FDA.

**Phase I/II studies**

In a phase II clinical trial, 111 patients with advanced, cytokine-refractory RCC received temsirolimus at doses of 25, 75 or 250 mg/week as a 30-min i.v. infusion [38]. Modest single-agent antitumour activity was demonstrated; the ORR was 7% (including one patient with a CR and seven patients with a PR) and 26% of patients had minor responses. The clinical benefit rate (CR + PR + minor response + SD ≥24 weeks) was 51%. Median TtP and OS were 5.8 and 15 months, respectively. The most commonly reported grade 3/4 AEs were hyperglycaemia, hypophosphataemia, anaemia and hypertriglyceridaemia.

Intravenous temsirolimus (5–25 mg/week) in combination with IFN-α (6–9 MU three times per week) has also been evaluated in a phase I/II dose escalation trial [39]. Of 71 assessable patients with metastatic RCC who had received 0–2 prior treatment regiments (prior IFN-α and/or temsirolimus was not permitted), PRs were achieved by 11% of patients and SD (≥24 weeks) by 30% of patients, and the median TtP was 9.1 months. The most common grade 3/4 AEs in the combination arm included leucopenia (28%), hypophosphatemia (18%), asthenia (18%) and anaemia (15%). In this study, the maximum tolerated dose was defined as 15 mg/week for temsirolimus and 6 MU three times per week for IFN-α.

**Phase III study**

A phase III study to assess the efficacy of temsirolimus alone and in combination with IFN-α compared with IFN-α alone as first-line therapy is being conducted in poor risk patients with advanced RCC [40]. Poor prognosis was defined as three or more of the following risk factors: lactate dehydrogenase >1.5 times upper limit of normal; haemoglobin less than the lower limit of normal; corrected calcium >10 mg/dl; time from diagnosis to first treatment <1 year; Karnofsky performance status of sixty to seventy; multiple organ sites of metastases. Patients were randomly assigned to IFN-α alone (up to 18 MU s.c. three times a week), temsirolimus (25 mg i.v. once a week) or temsirolimus (15 mg i.v. once a week) plus IFN-α (6 MU s.c. three times a week).

Preliminary results from an interim analysis indicate that the OS was significantly longer in patients treated with temsirolimus compared with IFN-α alone (10.9 months versus 7.3 months; P = 0.0069). However, there was no significant difference in OS between temsirolimus plus IFN-α compared with IFN-α alone (8.4 months versus 7.3 months; P = 0.6912). Temsirolimus as a single agent was better tolerated than IFN-α with a 16% reduction in the portion of patients with grade 3 or 4 AEs [40].

**Bevacizumab (Avastin®)**

Bevacizumab is a recombinant humanized mAb that inhibits tumour angiogenesis by targeting VEGF. Bevacizumab binds and neutralizes most biologically active isoforms of VEGFA, and has been approved by the EMEA and the FDA for the first-line treatment of advanced carcinoma of the colon or rectum in combination with i.v. 5-fluorouracil/folinic acid or 5-fluorouracil/folinic acid/irinotecan (EMEA guidelines) or with i.v. 5-fluorouracil–based chemotherapy (FDA guidelines). Bevacizumab in combination with carboplatin and paclitaxel is also indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.

**Phase II study (single-agent)**

In a randomized, placebo-controlled, phase II trial, patients previously treated with IL-2, with histologically confirmed clear-cell RCC, received either low- (5 mg/kg; n = 37) or high-dose (10 mg/kg; n = 39) bevacizumab, or placebo (n = 40),...
administered i.v. every 2 weeks [41]. Only four patients (4 of 39; ORR = 10%; 95% CI: 2.9 to 24.2) achieved an objective response (all PRs), including one patient with a PR for >1 year. In the bevacizumab arm, the median TtP was 4.8 months compared with 2.5 months in the placebo arm (P < 0.001). The HR for TtP favoured the low- and high-dose bevacizumab treatment groups (1.26; P = 0.053 and 2.55; P < 0.001, respectively) compared with TtP in patients in the placebo arm. No significant differences in OS were demonstrated.

There were no life-threatening AEs, as bevacizumab therapy was generally well tolerated. The most common grade 1/2 AEs were asymptomatic proteinuria, hypertension, malaise and epistaxis. Grade 3 hypertension (n = 8), asymptomatic proteinuria (n = 3) and chest pain (n = 2) were also reported.

**phase III study (first-line combination)**

Results from a phase III, randomized, controlled, double-blind trial recently reported at the 43rd annual meeting of the American Society of Clinical Oncology showed that the addition of bevacizumab to cytokine therapy improved median PFS in patients with metastatic RCC [42]. The phase III trial was conducted to evaluate the efficacy and safety of bevacizumab in combination with IFN-α as first-line treatment in this patient population. A total of 649 patients were randomly assigned 1:1 between the treatment arms, bevacizumab (10 mg/kg every 2 weeks) + IFN-α (9 MIU three times per week) (n = 327) versus placebo + IFN-α (n = 322). Patients received IFN-α plus bevacizumab or placebo until disease progression. Of the patients receiving treatment (n = 641), the median PFS for patients in the bevacizumab-containing arm was 10.2 versus 5.4 months in the IFN-α-only arm (HR = 0.63; P < 0.0001). The overall response rate (investigator assessed) was 31% for the bevacizumab arm, and 13% for the IFN-α-only arm (P < 0.0001). OS had not been reached in the bevacizumab arm at the time of the analysis, and was 19.8 months in the placebo/IFN-α arm (HR = 0.75; P < 0.267).

Safety and tolerability analysis indicated that there was an increased incidence of grade 3/4 AEs in the bevacizumab-containing group (all events: 60% versus 45%), and discontinuations due to AEs occurred at a higher rate in the bevacizumab arm than in the IFN-α-only arm (28% versus 12%, respectively). Most bevacizumab-related side-effects were consistent with previous observations.

**adjuvant treatment**

Since there is a high risk of recurrence in patients with locally advanced RCC, the use of an effective adjuvant therapy may reduce the risk of relapse and prolong survival in this patient population. The benefits of adjuvant cytokine therapy (IFN-α, IL-2) that have been reported in other tumour types have not been observed in RCC (Table 2). In a trial by Messing et al. [43], adjuvant IFN-α compared with observation had no effect on survival after radical nephrectomy. In another study, no significant differences in 5-year overall and event-free survival were observed with recombinant IFN-α and observation after radical nephrectomy [45]. Clark et al. [46] reported that there was no clinically meaningful benefit with high-dose bolus IL-2 administered postoperatively. In a prospectively randomized trial in RCC after nephrectomy, OS with adjuvant cytokine therapy was inferior to observation [44]. In view of these observations, there has been much interest in multtargeted agents such as sunitinib and sorafenib as suitable candidates for adjuvant therapy. These treatments have demonstrated efficacy in the metastatic setting are administered orally and generally have favourable tolerability profiles.

A number of factors require consideration when designing adjuvant therapy trials. These include prior surgery (partial versus radical nephrectomy); tumour histology (all histological subtypes versus clear cell); duration of therapy, dosage, sequence and frequency of surveillance; end points (disease-free survival and OS); opportunities to identify new markers for prognosis and challenges (patient selection criteria determine length and size of study; many adjuvant trials are ongoing and planned). Selecting the correct algorithm to assess the risk of recurrence of metastases is also critical to adjuvant study design. For example, the University of California Los Angeles Integrated Staging System (UISS) can be used to define subgroups on the basis of patients who are likely to benefit from adjuvant therapy [47]. This staging system has been evaluated in a study that included a total of 4202 patients with RCC from two centres in the United States (N = 1463) and six centres in Europe (N = 2739). Results from this study helped define the general applicability of the UISS for predicting survival in patients with RCC along different subsets of risk factors.

**ongoing adjuvant studies**

Three major, phase III, placebo-controlled trials evaluating sunitinib and sorafenib in the adjuvant setting are either planned or under way. ASSURE (Adjuvant Sorafenib Sunitinib...
Unfavourable REnal cell carcinoma) is a randomized, double-blind, placebo-controlled trial comparing sunitinib 50 mg/day (4 weeks on/2 weeks off) with sorafenib (400 mg twice daily) for 1 year; S-TRAC (Sunitinib Treatment in Renal Adjuvant Cancer) is a randomized, double-blind, placebo-controlled trial of sunitinib 50 mg/day (4 weeks on/2 weeks off) for 1 year and SORCE (SORafenib in patients with Resected primary renal CELl carcinoma at high or intermediate risk of relapse) is a double-blind trial comparing sorafenib 400 mg twice daily for 3 years, sorafenib 400 mg twice daily for 1 year followed by placebo for 2 years and placebo for 3 years. The primary end point is metastasis-free survival. The study is powered to detect an improvement in 3-year metastasis-free survival from 64% to 71%, following an average of 2 years’ treatment with sorafenib [48].

conclusions

Until recently, cytokine therapies have been considered the standard of care for patients with metastatic RCC. However, these agents generally do not offer a survival benefit and are associated with an increased risk of toxicity. Insights into the molecular pathobiology of RCC have led to exciting new developments and the introduction of targeted agents with unprecedented activity in this notoriously difficult-to-treat disease. Improved response rates and increased survival have been demonstrated with the multitargeted RTK inhibitors sunitinib and sorafenib as single-agent second-line therapy. In addition, results from a randomized phase III trial have indicated that sunitinib is significantly more effective than IFN-α in the first-line setting, while a phase III study of the mTOR inhibitor temsirolimus indicates that this agent may provide benefits in the first-line treatment of poor prognosis patients with metastatic RCC. The addition of bevacizumab to IFN-α therapy as first-line treatment has been shown to improve PFS in a randomized phase III study, and to improve TtP as second-line treatment in a smaller phase II study. These new agents have also typically demonstrated improved or equivalent tolerability profiles compared with cytokine therapy.

These results confirm that targeted inhibition of these single and multiple tumour targets is a feasible approach to treatment and provides a more positive outlook for the future management of metastatic RCC. Given the clinical experience with these agents in the metastatic setting, their role as adjuvant treatment is now being explored in a number of large-scale randomized trials in patients at risk of relapse following surgery. In addition to multitargeted RTK inhibitors, other targets being investigated include hypoxia-inducible factor and intracellular signal transduction targets involved in proliferation, survival and hypoxia stimulation. A number of promising agents are also undergoing phase I/II testing in combination with multitargeted RTK inhibitors, including VEGF-neutralizing antibodies [bevacizumab, VEGF-Trap, PDGF or fibroblast growth factor (FGF) antibodies] and other growth factor inhibitors (erlotinib, lapatinib, FGF, insulin-like growth factor, PDGF inhibitors). Results from these studies are awaited with anticipation.