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Current options for the treatment of locally advanced and metastatic renal cell carcinoma: focus on sunitinib

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ABSTRACT

Recent developments in molecular biology have increased our understanding of the biology and genetics of renal cell carcinoma (RCC) and identified pathways for novel targeted therapy. Several targeted therapies are now available that show promising activity in this disease. Sunitinib, an oral multitargeted tyrosine kinase inhibitor (TKI), has recently been approved for first-line treatment of metastatic RCC (mRCC) and is the new reference standard for the treatment of clear-cell disease. Three other promising TKIs are temsirolimus, approved for the treatment of advanced RCC, sorafenib, approved for the treatment of patients with advanced RCC who have failed or are considered unsuitable for cytokine therapy and bevacizumab, effective in combination with immunotherapy for first-line therapy of mRCC. Several other agents are under investigation as single-agent or combination therapy for mRCC. These include the TKIs axitinib, pazopanib, everolimus, erlotinib, gefitinib and lapatinib. Use of these agents is leading to the development of treatment paradigms that will transform the management of mRCC.

1. Introduction

Until recently, the only effective treatment for metastatic renal cell carcinoma (mRCC) was immunotherapy, with either interferon-alpha (IFN-α) or interleukin-2 (IL-2). However, recent developments in molecular biology led to dramatically increased understanding of the oncogenic transformation associated with clear-cell RCC [1] and the identification of rational targets for pharmacotherapy in clear-cell RCC. In this setting, inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene results in over-expression of several hypoxia-responsive proteins, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). [2] These growth factors act as agonists for their respective receptor tyrosine kinases (RTKs), VEGFR and PDGFR. Overexpression of these and other RTKs is implicated in tumour growth and angiogenesis [3] and a number of agents that inhibit one or more of these kinases have now been developed. One of these agents, sunitinib, is an orally bioavailable, multitargeted RTK inhibitor that targets the major subtypes of VEGFR (VEGFR-1, -2, and -3) and PDGFR (PDGFR-α and -β), stem cell factor receptor (c-KIT), colony stimulating factor receptor type 1 (CSF-1R), Fms-like tyrosine kinase-3 receptor (FLT3), and the glial cell-line derived neurotrophic factor receptor (RET). [4–7] Sunitinib has demonstrated superior efficacy to IFN-α in first-line therapy of mRCC, and is the new reference standard for the treatment of this condition. [8] This review describes current treatment options for first- and second-line treatment of mRCC, with a focus on sunitinib.

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2. First-line therapy of mRCC

2.1. Immunotherapy

Although cytokines have been in use for more than 20 years, the efficacy of these agents in mRCC remains controversial. Overall response rates in RCC are low (5%–20%), median overall survival (OS) is approximately 12–17 months,[9–12] and both cytokines are associated with significant toxicity that often limits their use.[13] In patients with mRCC of intermediate prognosis, the most recent data from the French Immunotherapy Intergroup's PERCY Quattro trial showed that cytokine therapy (IFN-α, IL-2 or the combination) provided no survival benefit compared with medroxyprogesterone.[14]

Nonetheless, small numbers of patients have been shown to benefit from treatment.[15,16] These patients have typically undergone nephrectomy, have an Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status of 0 and a single metastatic site.[11,17] In addition, decreased carbonic anhydrase IX (CAIX) expression occurs in tumours with the highest malignant potential, and CAIX expression $\leqslant$85% has been identified as an independent poor prognostic factor for survival during IL-2-based immunotherapy in patients with mRCC.[18,19]

In selected patients with clear-cell mRCC and good performance status, major tumour regressions and complete responses have been reported with IL-2 therapy.[12] In some cases, complete response was maintained throughout long-term follow-up (>10 years).[12] Hence, although its curative potential is limited to a small proportion of patients, immunotherapy is the only systemic therapy shown to cure patients in mRCC. The updated European Association of Urology (EAU) guidelines on RCC state that only selected patients with mRCC, with a good risk profile and clear-cell subtype histology, derive clinical benefit from immunotherapy with IL-2 or IFN-α (grade B recommendation).[20] The guidelines also note that combinations of cytokines do not improve OS compared with monotherapy (grade A recommendation).[20]

2.2. Sunitinib

On the basis of the impressive activity and favourable safety profile of sunitinib, demonstrated in two phase II studies in patients with cytokine-refractory mRCC,[21,22] a multicentre, randomised phase III study comparing sunitinib with IFN-α as first-line therapy was initiated.[8] A total of 750 patients with clear-cell mRCC were randomised to receive oral sunitinib ($n = 375$) at a dose of 50 mg/day in repeated 6-week cycles consisting of 4 weeks on treatment followed by 2 weeks off treatment (the 4/2 schedule), or IFN-α ($n = 375$) by subcutaneous injection three times per week at 3 MU per dose in the first week, 6 MU per dose in the second week and 9 MU per dose in all subsequent weeks. The primary endpoint was progression-free survival (PFS); secondary endpoints included objective response rate (ORR), according to the Response Evaluation Criteria in Solid Tumours (RECIST),[23] OS and safety.

Sunitinib treatment resulted in a statistically significant improvement in both PFS and ORR.[8] Median PFS was 11 months in the sunitinib group compared with 5 months in the IFN-α group (as assessed by independent central review), corresponding to a hazard ratio (HR) of 0.42 (95% confidence interval [CI]: 0.32–0.54; $p < 0.001$). The ORR was 31% for the sunitinib group (95% CI: 26–36) and 6% for the IFN-α group (95% CI: 4–9; $p < 0.001$), assessed by independent central review. There was a trend toward improved survival with sunitinib; 13% of patients in the sunitinib group and 17% in the IFN-α group had died (HR for death, 0.65; 95% CI: 0.45–0.94; $p = 0.02$). At the time of analysis, median OS had not been reached in either treatment group; final OS results will be reported. These data complement the findings of the second-line phase II trials and establish sunitinib as the new reference standard for first-line treatment of clear-cell mRCC.

Importantly, an analysis of prognostic factors using updated results from the phase III trial of sunitinib in first-line treatment of mRCC showed that the benefit of sunitinib with respect to PFS extends across all Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk factor groups (HR: 0.488; 95% CI: 0.406–0.586).[24] In patients with no risk factors (favourable risk), median PFS was 14 months (95% CI: 11–16) for sunitinib versus 8 months (95% CI: 7–10) for IFN-α. In patients with one or two risk factors (intermediate risk), median PFS was 9 months (95% CI: 8–11) for sunitinib versus 4 months (95% CI: 4–4) for IFN-α; and in those with three risk factors (poor risk), median PFS was 4 months (95% CI: 2–10) for sunitinib versus 1 month (95% CI: 1–2) for IFN-α. This analysis has led to the development of a nomogram designed to help predict, in an individual patient, the likelihood of PFS after 12 months of sunitinib treatment, based on pre-treatment features displayed by the patient. This is discussed in the accompanying article in this supplement entitled 'Key considerations for the use of targeted therapy in patients with mRCC'.

A second recent analysis examined the exposure–response relationships of sunitinib in mRCC.[25] In this study, Houk et al. used pharmacokinetic and efficacy data from four phase II and III clinical trials in untreated and cytokine-refractory mRCC. Steady state area under the curve (AUCss) was used as a measure of exposure. The results indicate a significant association between sunitinib exposure and longer time to progression (TTP) and improved OS in patients with mRCC. In these patients, odds ratios suggest a 2.6-fold increase in the frequency of partial response for each unit increase in AUCss. A tumour growth dynamics model was also developed to

describe changes in tumour volume during treatment as a function of AUCss. Based on this model, clinical trial simulations assuming perfect patient compliance predict that 62% of patients would achieve a partial response during treatment with sunitinib 50 mg/day. These data on the exposure–response relationships in mRCC suggest increased sunitinib exposure is associated with clinical benefit.

2.3. Sorafenib

Sorafenib is an oral, multitargeted kinase inhibitor targeting VEGFR-2 and -3, PDGFR-β, FLT3, c-KIT, RET, B-Raf and Raf-1/C-Raf.[26,27] Sorafenib was approved for the treatment of advanced RCC in patients previously treated with cytokines on the basis of data from phase II and phase III clinical trials.[28–30] In a recent phase II randomised trial of first-line sorafenib compared with IFN-α in patients with advanced RCC, PFS did not differ significantly between the two treatment groups (median PFS 5.7 months versus 5.6 months for sorafenib and IFN-α, respectively), resulting in an HR of 1.14 (95% CI: 0.613–1.272; $p = 0.504$).[31] However, these results differ from those obtained in an ongoing expanded access programme. In this setting, median PFS in patients receiving first-line sorafenib ($n = 224$) was 35.1 weeks (95% CI: 32.7–41.9).[32] Similarly, preliminary results from a randomised phase II study of first-line sorafenib compared with sorafenib plus low-dose IFN-α in mRCC suggest a median TTP of 9.3 months in each treatment group.[33]

2.4. Bevacizumab

Bevacizumab is a humanised monoclonal antibody that binds and neutralises all major isoforms of VEGF-A[34] First-line bevacizumab therapy has been evaluated in a randomised, controlled, double-blind phase III study in 649 patients with clear-cell mRCC receiving IFN-α2a.[35] This trial evaluated the addition of bevacizumab (10 mg/kg until progression) to IFN-α2a (9 MU, three times a week for 12 months) on OS, PFS and ORR and safety outcomes. The addition of bevacizumab to IFN-α2a significantly increased PFS (10.2 versus 5.4 months; HR = 0.63; $p < 0.0001$) and ORR (30.6% versus 12.4%; $p < 0.0001$) compared with IFN-α2a alone.

The efficacy of first-line bevacizumab, with or without erlotinib, has also been evaluated in a randomised, double-blind, phase II trial in patients with mRCC with >50% clear-cell histology and previous nephrectomy ($n = 104$).[36] In the bevacizumab group ($n = 53$), ORR was 13% and PFS was 8.5 months. The addition of erlotinib did not appear to improve the efficacy of bevacizumab, and ORR and PFS in the two groups were similar. To date, no phase III trial has been undertaken to evaluate bevacizumab alone in comparison with bevacizumab-based therapy in RCC.

2.5. Temsirolimus

Temsirolimus, a mammalian target of rapamycin (mTOR) kinase inhibitor administered via a once weekly intravenous infusion, is effective in patients with poor-risk mRCC, P,[37,38] and was recently approved for the treatment of advanced RCC. In the pivotal phase III trial, patients with poor-risk mRCC were randomised to receive first-line therapy with temsirolimus alone ($n = 209$), IFN-α alone ($n = 207$) or the combination ($n = 210$).[38] Overall survival was significantly longer in the temsirolimus group (median OS 10.9 months; 95% CI: 8.6–12.7) than in the IFN-α group (median OS 7.3 months; 95% CI: 6.1–8.9), with an HR of 0.73 (95% CI: 0.57–0.92; $p = 0.0069$). However, OS in the combination group (median OS 8.4 months; 95% CI: 6.6–10.2) was not significantly different from that with IFN-α alone. An analysis of the influence of tumour histology and age on treatment outcome suggested that although the benefit of temsirolimus was seen in patients with clear-cell and non-clear cell histology, the benefit of temsirolimus is more pronounced in those with non-clear cell RCC.[39] This difference may be because cytokines are less active in non-clear cell RCC. Temsirolimus prolonged median OS and PFS in patients less than 65 years of age, but no benefit was seen in those aged $\geqslant$65 years.[39] Although this analysis also examined the efficacy of temsirolimus in intermediate-risk patients compared to those with poor-risk, low patient numbers preclude any meaningful conclusions. It should also be noted that the risk criteria used in this trial differ from MSKCC criteria; the number of metastatic sites, not a validated MSKCC parameter, has been added to the five previously validated factors. It should also be considered that temsirolimus can be associated with adverse events including hyperglycaemia or glucose intolerance, interstitial lung disease and hyperlipidaemia.[40]

3. Second-line therapy of mRCC

3.1. Sunitinib

Approval of sunitinib was based on data from two consecutive, independent, open-label phase II studies in patients with cytokine-refractory mRCC.[21,22] The similar design of the trials permitted a subsequent independent analysis of the pooled data ($n = 168$). The ORR and PFS observed were similar in each trial, and the most recent analysis of pooled, updated efficacy data showed an ORR of 45% (95% CI: 39–54), median PFS of 8.4 months (95% CI: 7.9–10.7) and median OS of 22.3 months (95% CI: 14.8–36.0).[41] The median survival with second-line sunitinib compares favourably with historical experience (12.7 months) in second-line therapy with other agents.[42]

RCC tumour resistance to bevacizumab may be partly driven by pathways that are sensitive to inhibition by

sunitinib. This hypothesis was tested in a phase II study of sunitinib (50 mg daily, 4/2 schedule) in bevacizumab-refractory mRCC, defined as disease progression (as per RECIST) within 3 months of bevacizumab-based therapy.[43] Among 61 evaluable patients, 14 patients (23%; 95% CI: 13–36) achieved a partial response, and median PFS was 30.4 weeks (95% CI: 18.3–35.6). These data suggest that sunitinib may inhibit signalling pathways involved in bevacizumab resistance, although additional studies are needed to determine the precise mechanism of response to sunitinib.

In addition, preliminary data from a recent retrospective analysis may indicate a lack of cross-resistance between sunitinib and sorafenib. In this study, among 56 patients achieving a partial response or stable disease to first-line sorafenib, 30 patients exhibited a partial response or stable disease when treated with second-line sunitinib.[44]

The results of the ongoing sunitinib expanded-access study in patients with cytokine-refractory or intolerant mRCC provide further information on clinical outcomes in a diverse patient population.[45] Patients are treated with sunitinib 50 mg/day on the 4/2 schedule. Among 2,341 evaluable patients, the ORR was 9.3%, with a further 43.1% of patients exhibiting stable disease for more than 3 months. In 1,840 patients with prior cytokine therapy, median PFS was 8.9 months (95% CI: 8.3–9.9). Patients with a favourable prognosis (based on modified MSKCC risk criteria) had a longer median PFS compared with those with intermediate or poor prognosis. Sunitinib was active in subgroups not previously studied, including those with brain metastases ($n = 182$; ORR 7.1%; median PFS 5.5 months), non-clear cell histology ($n = 276$; ORR 5.4%; median PFS 6.7 months), or ECOG performance status $\geqslant 2$ ($n = 308$; ORR 4.2%; median PFS 4.4 months). Sunitinib was associated with acceptable tolerability in the expanded access trial, regardless of age, performance status, or site of baseline metastatic disease, and showed a safety profile similar to that reported in the registration programme[21,22]; see also the article by Négrier and Ravaud in this supplement.

The activity of sunitinib administered in a continuous dosing regimen has been assessed in 107 patients with cytokine-refractory mRCC.[46] Patients were randomised to receive sunitinib once daily either in the morning ($n = 54$) or in the evening ($n = 53$), at a starting dose of 37.5 mg. Twenty-one patients (20%) achieved a partial response and median PFS was 36 weeks (95% CI: 28–44). There were no significant differences with respect to tolerability between those treated in the morning or evening. The results show that sunitinib continuous dosing has potential for second-line therapy in mRCC, providing an alternative regimen that can be explored in combination studies.

Several phase I studies have explored, or are currently investigating the feasibility of combining sunitinib with other agents. One of these tests the hypothesis that the combination of bevacizumab and sunitinib may increase antitumour efficacy by maximising inhibition of the VEGF pathway. In this phase I dose-finding trial, 16 patients with mRCC received escalating doses of sunitinib (25–50 mg/day in a 4/2 schedule) with fixed-dose bevacizumab (10 mg/kg) every 2 weeks continuously.[47] Sunitinib 25 mg/day plus bevacizumab 10 mg/kg was tolerable in mRCC patients and further testing of this combination in phase II trials may be indicated.

A second phase I study will assess the combination of sunitinib plus gefitinib, an inhibitor of epidermal growth factor receptor (EGFR), in mRCC.[48] Patient accrual to a phase II portion of this study is underway. In addition, two phase I studies in patients with advanced solid tumours (including RCC) are ongoing; these will evaluate sunitinib combined with docetaxel[49] and sunitinib combined with capecitabine.[50]

3.2. Sorafenib

Clinically relevant activity of sorafenib in patients with mRCC was first reported in a phase II randomised discontinuation trial.[28] This study was followed by a randomised, placebo-controlled phase III trial in patients with mRCC who had failed cytokine therapy.[29,30] At crossover, investigator-assessed PFS in 903 patients was significantly longer in the sorafenib group compared with the placebo group (5.5 months versus 2.8 months; $p < 0.001$).[51] This benefit was independent of age, MSKCC score, previous cytokine therapy, presence of liver or lung metastases and the time since diagnosis (<1.5 versus $\geqslant$1.5 years).[51] Of these 903 patients, 1 (<1%) patient in the sorafenib group demonstrated a complete response. Partial response was seen in 43 (10%) patients in the sorafenib group and 8 (2%) in the placebo group.[51] Patients were subsequently unblinded, and those receiving placebo were allowed to cross over to sorafenib; 216 of the 452 patients originally randomised to placebo did so. At a pre-planned secondary interim analysis, censoring of crossover data showed a significant difference in OS (median OS 19.3 months for sorafenib versus 15.9 months for placebo; HR 0.77; 95% CI: 0.63–0.95; $p = 0.015$).[30] The intent-to-treat OS analysis did not reach pre-specified levels of significance, suggesting a confounding effect of crossover. At the final analysis, OS for the intent-to-treat population did not differ significantly between sorafenib (median OS 17.8 months) and placebo (median OS 15.2 months; $p = 0.146$).[30] Sorafenib has also been investigated in a large, open-label, expanded-access trial in patients with advanced RCC.[52] In an analysis of the 1,850 patients evaluable for efficacy, the ORR was 3.7%. Stable and progressive disease occurred in 1,479 (79.9%) and 303 (16.4%) patients, respectively. Assessment of PFS was limited by the short median duration of treatment (12.3 weeks).

3.3. Bevacizumab

Bevacizumab has also shown activity as second-line treatment for mRCC. The efficacy of high- and low-dose bevacizumab was compared in a randomised, placebo-controlled phase II study in patients with clear-cell mRCC, of whom 88% had been previously treated with IL-2.[53] High-dose bevacizumab significantly prolonged TTP compared with placebo (median TTP 4.8 months versus 2.5 months; HR 2.55; $p < 0.001$); the difference in TTP between low-dose bevacizumab and placebo was not significant (HR 1.26; $p = 0.053$). There were no differences in OS between the treatment groups, partly because the trial was terminated early following observation of an increase in PFS.

3.4. Axitinib

Axitinib is an imidazole derivative that inhibits the tyrosine kinase portion of all VEGFRs and PDGFR-β at low nanomolar concentrations.[54] In a phase II study of patients with cytokine-refractory mRCC ($n = 52$), axitinib at a dose of 5 mg twice daily induced partial response in 21 patients (40%).[55] In a more recent phase II study of axitinib (5 mg twice daily) in patients with sorafenib-refractory mRCC, partial response was observed in 6 of the 42 evaluable patients (14%) and stable disease observed in 15 patients (36%). Disease progression occurred in 12 patients (29%) and 9 patients (21%) withdrew due to adverse events.[56]

3.5. Pazopanib

Pazopanib is another oral, multitargeted kinase inhibitor of all three VEGF receptors, PDGFR-α/β and c-Kit.[57,58] In a randomised discontinuation trial, 225 cytokine-naïve or cytokine/bevacizumab-refractory patients with advanced or metastatic RCC received pazopanib 800 mg once daily for 12 weeks.[58] Those who experienced partial or complete response continued pazopanib treatment and those with stable disease were randomised to continue either pazopanib or placebo. At baseline, 67% of patients were treatment-naïve and 33% had failed one prior treatment regimen. Independent review of the first 60 patients showed that 24 (40%) patients had partial response, 25 (42%) had stable disease and 5 (8%) had progressive disease.[58] A randomised phase III, placebo-controlled trial of pazopanib in approximately 350 patients with locally advanced and/or metastatic clear-cell RCC is ongoing.

3.6. Everolimus

Everolimus (RAD001), an oral mTOR inhibitor, has shown activity in a phase II trial of patients with mRCC.[59] In this trial, patients with no more than 1 prior therapy ($n = 41$) received everolimus 10 mg/day in a 28-day cycle. Twelve patients (23%) exhibited a partial response and 19 (46%) had stable disease for more than 3 months; median OS was 11.5 months. Everolimus is also under investigation in a randomised phase III trial in patients with mRCC that has progressed during treatment with sunitinib and/or sorafenib.

3.7. Lapatinib

The efficacy of lapatinib, a dual inhibitor of EGFR (ErbB-1) and ErbB-2 type I RTKs, has been compared with hormone treatment (tamoxifen and megestrolacetate) in a phase III study in patients with advanced RCC after failure of first-line cytokine therapy.[60] Randomisation was stratified by tumour EGFR expression (EGFR overexpressed or not). Overall, median TTP and median OS did not differ significantly between the two treatment groups. However, patients with high tumour EGFR expression (3+ by immunohistochemistry), who comprised 58% of the total randomised, showed a trend towards improved median TTP in the lapatinib group, and median OS was significantly longer in these patients (46.0 weeks) than in similar patients receiving hormone treatment (median OS 37.9 weeks; HR 0.69; $p = 0.02$). This study shows that patient selection may be important to optimise lapatinib treatment.

4. Future trials and role of new agents in adjuvant therapy

Patients with locally advanced disease have a high risk of recurrence, and an effective adjuvant therapy may reduce the risk of relapse and prolong survival. Adjuvant cytokine therapy has not proved beneficial in RCC to date.[61,62] Although adjuvant treatment with an autologous renal tumour cell vaccine has been reported to reduce the risk of recurrence in RCC patients after radical nephrectomy,[63] the results of this trial must be interpreted with caution because of substantial biases resulting from the randomisation process.

Multitargeted, orally administered agents such as sunitinib and sorafenib, with demonstrated efficacy in the metastatic setting and generally favourable tolerability profiles, may be suitable candidates for adjuvant therapy. Three major, phase III, placebo-controlled trials evaluating sunitinib and sorafenib in the adjuvant setting are either planned or underway. The ASSURE (Adjuvant Sorafenib Sunitinib Unfavourable REnal cell carcinoma) trial, sponsored by several US cooperative groups, will compare disease-free survival in 1,332 patients randomised to receive sunitinib (50 mg/day via the 4/2 schedule) plus placebo, sorafenib (400 mg twice daily) plus placebo, or placebo for both sorafenib and sunitinib, following radical or partial nephrectomy. Accrual began in April 2006 in centres across the US and Canada. Treatment continues for up to 54 weeks in the absence of disease progression or unacceptable toxicity, after which patients will be followed for 9 years.

In the SORCE trial (SOrafenib in patients with Resected primary renal CEll carcinoma at high or intermediate risk of relapse), run jointly by the UK Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC), patients are randomised in a ratio of 3:3:2 to receive sorafenib 400 mg twice daily for 3 years, sorafenib 400 mg twice daily for 1 year followed by placebo for 2 years, or placebo for 3 years. [13,64] The primary endpoint is disease-free survival, with the study powered to detect an improvement in 3-year metastasis-free survival from 64%–71% after an average of 2 years of treatment with sorafenib. The trial will recruit 1,656 patients with resected primary RCC at intermediate or high risk of relapse.

S-TRAC (Sunitinib Trial in Adjuvant Renal cancer Treatment), a worldwide study primarily conducted in Europe, will randomise 228 patients with high-risk T3, T4 or node-positive disease to sunitinib 50 mg/day (4/2 schedule) or placebo for 1 year after surgery, with disease-free survival as an endpoint.

In addition to the above adjuvant trials, several small pilot and phase II trials are ongoing or planned to investigate the effect of neoadjuvant single-agent sorafenib, sunitinib and bevacizumab, respectively, in RCC patients undergoing surgery.

5. Conclusion

Recent advances in understanding the pathogenesis of RCC have led to the development of targeted therapy. Results with several of these targeted agents confirm that inhibiting multiple tumour targets is a viable and effective approach to treatment, offering an improved outlook for the future management of RCC.

The significant improvement in PFS observed with sunitinib compared with IFN-α as first-line therapy for patients with mRCC indicates that sunitinib is the new reference standard in this setting. Sunitinib is suitable for all patients with mRCC; the benefits of treatment have been shown to extend across all MSKCC prognostic risk factor groups, and the expanded access programme has shown that sunitinib is active in RCC patients with non-clear cell histology, in those with brain metastases, and in those with poor performance status. A phase III study of the mTOR inhibitor temsirolimus suggests that this agent also provides benefits in first-line treatment of poor prognosis patients. Furthermore, preliminary data suggest combination therapy with IFN-α plus bevacizumab may provide another option in first-line mRCC therapy.

In the second-line setting, sunitinib offers substantial efficacy in cytokine- and bevacizumab-refractory RCC and there is some evidence to support its use in sorafenib-refractory advanced RCC. Sorafenib and bevacizumab are also effective in patients with cytokine-refractory mRCC. Further studies exploring various combinations of these targeted treatments in differing sequences are needed to optimise treatment in both the first and second-line setting. Given the activity and acceptable tolerability of sorafenib and sunitinib in the metastatic setting, their role in the adjuvant setting is now being investigated in patients at risk of relapse following surgery.

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Conflict of interest

A. Ravaud: member of the Global, European and/or French advisory boards of Pfizer, Bayer, GSK and Wyeth. Member of RCC clinical trial steering committees for Pfizer and Novartis. Principal investigator for the S-TRAC trial sponsored by Pfizer.

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