Practice Points

- There is a need for effective adjuvant treatment in renal cell carcinoma (RCC). Significant proportions of patients remain at high risk of recurrence after surgery, particularly those with stage III disease. Two main scoring systems are available for predicting progression after surgery: the UCLA integrated scoring system and the Mayo Clinic stage, size, grade and necrosis nomogram (also known as the Leibovich score or modified stage, size, grade and necrosis score).

- Trials of nontargeted agents have not shown clinical benefit within the adjuvant setting. This includes treatment with IFN-α, IL-2 and tumor-targeted vaccines.

- Several large-scale, multicenter, randomized trials are ongoing in adjuvant treatment of RCC. These include trials with the receptor tyrosine kinase inhibitors sunitinib, sorafenib and pazopanib, in addition to the mTOR inhibitor everolimus. Successful modifications have been made to the trial protocols to take account of higher than expected drop-out rates, mainly caused by treatment-related toxicity.

- Improvements are needed in clinical trial design to ensure agents are more quickly and cost-effectively tested in the adjuvant setting. Many potential agents and combinations of different agents (immunomodulators, antiangiogenic agents and other signaling inhibitors) remain to be tested in the clinical setting in RCC. Multiarm, multistage clinical trial designs offer design strategies for more efficient trials of adjuvant therapy in RCC. A reliable biomarker of RCC activity would be a useful surrogate of benefit to accelerate progress in clinical trials.

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SUMMARY  Twenty to thirty percent of patients with stage I–III renal cell carcinoma will relapse within 5 years of surgery. Recent advances in our understanding of the molecular pathogenesis of renal cell carcinoma have led to several large randomized clinical trials investigating the role of molecularly targeted agents in the adjuvant setting. However, there are higher than expected drop-out rates due to the intolerability of side effects compared with treatment given in the metastatic setting. Additionally, significant challenges remain in the area of clinical trial design and the need to assess multiple potential therapies in a time- and cost-efficient manner, and to identify which patients are likely to benefit from adjuvant therapy.

Renal cell carcinoma (RCC) is the tenth most common cancer worldwide and its incidence has been rising steadily [1]. In the EU, 63,300 new diagnoses and 26,400 deaths were reported in 2006 and the incidence of RCC doubled in the period from 1975 to 2005 [2]. This may, at least in part, be due to increased rates of renal tumors being discovered incidentally on radiologic imaging performed for an unrelated reason [3]. The increase in medical imaging over the last decades has also allowed for the discovery of early-stage RCC in patients who are asymptomatic. However, this does not fully explain the increases seen for RCC overall, as although the greatest increase in incidence has been seen for localized tumors, there have also been increases in more advanced tumors [3]. This has also contributed towards rising rates of mortality [2]. Rising rates of obesity and hypertension (established risk factors for RCC) have been postulated to contribute. The upward smoking prevalence in earlier decades might also have contributed to the continuing increases in RCC, particularly at older ages [3].

Surgery is the standard treatment for early-stage RCC. If feasible, nephron-sparing surgery with optional regional lymph node dissection is the procedure of choice, or either an open or laparoscopic nephrectomy [4,5]. Radical surgery can be curative. In a recent analysis of the National Cancer Data Base (USA), 50.6% of patients had stage I RCC, 26.7% stages II and III and 22.7% had stage IV RCC at presentation [6]. While the prognosis for stage I RCC is excellent, the risk of relapse in patients with stages II and III is high, with 20–30% of all patients with stage I–III RCC experiencing relapse after surgical excision [6]. The median time to relapse after surgery is 1–2 years with the majority occurring within 3 years after initial diagnosis.

Patient selection is therefore an essential consideration when discussing the potential role of adjuvant therapy in RCC. It is clear that patients with a lower risk of relapse need to be spared from unnecessary treatments, while those with a higher risk of recurrence may be more likely to benefit from adjuvant therapy. Several prognostic, retrospectively validated nomograms exist that assess relapse risk in patients with resected RCC: the UCLA integrated scoring system (UISS) and the Mayo Clinic size, grade and necrosis nomogram (also known as the Mayo score, Leibovich score or the modified stage, size, grade and necrosis score) [7]. These scores are particularly useful to aid appropriate patient selection and to help to identify those patients most likely to benefit from adjuvant treatment.

The UISS stratification is based on the 1997 tumor, nodes and metastases score, Fuhrman grade and Eastern Cooperative Oncology Group performance status and allows the classification of patients into low-, intermediate- and high-risk groups for developing recurrence or metastases after treatment of localized or locally advanced RCC [8,9]. This score includes all histologic subtypes of RCC. It is limited by the complexity and technical demands of obtaining molecular markers from all patients. The UISS is currently recommended by the National Comprehensive Cancer Network to assist in identifying patients for adjuvant trials.

The Leibovich score is calculated using an algorithm that includes tumor stage, regional lymph node status, tumor size, nuclear grade and histologic tumor necrosis to predict metastasis-free survival in patients postnephrectomy with clinically localized clear cell RCC [10,11]. The authors originally included 1801 patients with a mean follow-up of 9.7 years and showed statistically significant associations between calculated score and progression to metastatic RCC. The
Leibovich score predicts that 10-year survival is 92.5, 64.3 and 23.6% for patients with low (scores of 0, 1 and 2), medium (scores of 3–5) or high (scores of 6 or above) risk, respectively, of developing metastases after nephrectomy. This highlights the need to investigate potential therapies to reduce the risk of metastases, particularly in medium- and high-risk patients. A potential limitation of the score is its reliance on histologic tumor necrosis, which does not have a standardized definition, consensus for reporting or availability at many centers. It should be noted that the Leibovich score is also applicable only to patients with clear cell RCC. The Leibovich score was shown to be slightly superior to the UISS nomogram in one validation study of 388 patients with an accuracy of 0.830 compared with 0.760 [12].

There is currently no evidence from properly designed randomized controlled trials to support the use of adjuvant treatment in localized RCC. However, several large randomized clinical trials are currently investigating the role of new targeted agents in the adjuvant setting after successes in treating metastatic RCC. This article aims to briefly review past and present trials of adjuvant treatment in RCC and suggest what can be learnt from these experiences for the future of adjuvant treatment in RCC.

## Trials of ‘nontargeted’ agents in the adjuvant setting

In the last 30 years, only a few drugs have shown some activity against advanced renal cancer. Figure 1 shows drugs licensed for treatment of metastatic RCC. Immunomodulators such as IFN-α and IL-2 were initially used to control metastatic RCC, stabilizing the disease for several years or occasionally curing it completely [13,14]. Such exceptional (although relatively infrequent) results initiated trials of immunomodulators in the adjuvant setting. A modest benefit in survival was reported with IFN-α and with IL-2 therapy in the context of metastatic RCC, but these immune modulators do not currently have a defined role in the adjuvant setting. In randomized trials, adjuvant IFN-α and recombinant IFN-α2b have been shown to not contribute to survival or relapse-free survival [15,16]. For example, a Phase III trial investigating adjuvant IL-2 in high-dose bolus form was closed early because an interim analysis revealed that disease-free survival (DFS) was not affected [17]. In a subsequent study, adjuvant IL-2 in low-dose subcutaneous form was also shown to be ineffective with respect to prolonging DFS [18]. Whether the lack of effectiveness of immunomodulators in the adjuvant setting was due to the low objective response rate (even in the metastatic setting), patients being included despite being at low risk of recurrence,
or whether insufficient follow-up was performed to see an effect, is unclear.

A more gentle method of immunomodulation and its application to adjuvant therapy in RCC has come in the form of tumor vaccines. Galligioni et al. investigated the use of autologous irradiated tumor cells mixed with bacillus Calmette–Guérin as an adjuvant strategy and found no statistically significant improvement in overall survival (OS) or DFS [19], but a multicenter, Phase III, randomized controlled trial of adjuvant autologous tumor cell vaccine conducted in Germany showed a statistically significant DFS benefit [20]. In the latter investigation, 379 patients with pT2–3b pN0–3 M0 disease were included in the analysis and 5-year progression-free survival (PFS) was 77.4% and 67.8% in the vaccine and the control groups, respectively. That study, however, has been widely criticized because 174 patients were lost to follow-up after randomization and also because differences in OS were not analyzed.

Another vaccine strategy has focused on the use of heat shock proteins. The heat shock protein peptide complex HSPPC-96 (vitespen) was developed from autologous tumors in RCC. Following encouraging results in a Phase II trial, a 728-patient, multicenter, open-label, randomized Phase II trial compared adjuvant HSPPC-96 with observation following nephrectomy and found no difference in recurrence-free survival after a median follow-up of 1.9 years [21].

The use of hormonal therapy has also been explored as a potential adjuvant treatment of high-risk RCC. In a prospective randomized study of 136 patients, medroxyprogesterone acetate was found to provide no benefit with regard to disease recurrence and was associated with significant toxicity [22].

Therefore, currently no adjuvant therapies have shown clear evidence of DFS improvement [16,23] and active surveillance has remained the standard of care after partial or radical nephrectomy. However, these trials demonstrated that large, multicenter trials are feasible and that well-powered trials that look for statistical differences in DFS and OS are possible in the adjuvant setting in renal cancer.

Rationale for investigating targeted agents in the adjuvant setting in RCC

Recent advances in our understanding of the molecular pathogenesis of RCC have led to the successful development of new therapeutic strategies for the treatment of metastatic RCC. Central to the biology of sporadic RCC is loss of function of the von Hippel–Lindau (VHL) tumor suppressor gene, located on chromosome 3p (reviewed in [24]). VHL was identified in patients with familial VHL disease, an autosomal dominant cancer syndrome associated with the development of a number of tumors including conventional RCC [25]. Recent comprehensive genetic studies suggest very high rates (>95%) of VHL involvement through mutation, methylation and loss of heterozygosity analysis, such that VHL loss of function might provide a molecular basis for classification as clear cell RCC [26,27]. The VHL gene product functions in the hypoxia inducible factor (HIF) pathway, forming a multiprotein complex that principally functions by ubiquitinating HIF-α leading to its proteasomal degradation [28,29]. Since the expression of the HIF pathway is primarily controlled by levels of HIF-α subunits, loss or inactivation of VHL leads to high levels of HIF-α subunits, and increased activity of the HIF pathway [27–31].

HIF is a transcription factor that co-ordinates the response of cells to low oxygen levels and is critical for tumor cell survival (reviewed in [32]). In response to low oxygen levels, HIF stimulates up to 100 genes, which increase cellular metabolism and cell survival pathways, and activate angiogenesis (new blood vessel formation) to improve oxygenation and nourishment. This includes VEGF, which results in RCCs being characterized as highly vascular tumors.

Therapies targeting this pathway (so-called ‘targeted’ therapies) have proven a highly effective therapeutic strategy in RCC, improving the outlook for patients with advanced disease (reviewed in [33]). Inhibition of the VEGF pathway has been achieved via monoclonal antibodies targeted to bind VEGF (bevacizumab) or through intracellular inhibition of VEGF signaling through the use of small molecule tyrosine kinase inhibitors (TKIs) that target the intracellular kinase domains of the VEGF receptors (VEGFR1–3), such as sorafenib, sunitinib, pazopanib and axitinib [34–40]. Receptor tyrosine kinases are essential for the transduction of extracellular signals into the cell. Studies have shown improvement of PFS and OS resulting in regulatory approval to treat patients with metastatic RCC with these drugs.

Levels of HIF-α (and VEGF) have also been shown to be increased in RCC via activation of the mTOR–PI3K pathway [40–42]. Agents targeting
mTOR, such as temsirolimus and everolimus, also exert antiangiogenesis effects and have been approved to treat patients with metastatic RCC [43,44]. In patients who have progressed on first-line therapy with a VEGF pathway antagonist, everolimus has been shown to offer clinical benefit (modest prolongation of PFS compared with placebo in a randomized Phase III study) [44,45].

Overall, targeted drugs have a relatively favorable toxicity profile in the advanced disease setting and are usually orally bioavailable (reviewed in [33]). Therefore, encouraged by positive outcomes in the metastatic setting, targeted therapies are being tested in the adjuvant setting. Six large-scale, randomized trials are in progress (Table 1):

- The S-TRAC trial is a double-blind, randomized, multicenter study comparing sunitinib with placebo in 720 patients at high risk of relapse (based on UISS criteria) after nephrectomy [101]. The primary end point is DFS and the study will be completed in 2015;

- The SORCE trial is a double-blind, randomized, multicenter study with three treatment arms comparing treatment with sorafenib for 1 year versus treatment with sorafenib for 3 years versus treatment with placebo [102]. The study will include 1656 patients with resected RCC with intermediate and high risk of developing metastatic disease, based on the Leibovich score (score of 3–11). The primary end point is DFS and recruitment to the study is expected to be completed in 2013;

- The ASSURE trial is a double-blind, randomized, multicenter study comparing treatment with placebo versus sorafenib or sunitinib [103]. The study will include 1923 patients with pT1b–4 tumors or with fully resected node-positive disease. Patients will be stratified into high- and very-high-risk groups. The primary end point is DFS, with OS and translational studies as secondary end points. This trial is in the process of reporting;

- The SWOG-S0931 trial is a double-blind, randomized, multicenter study comparing treatment with everolimus for 1 year versus placebo [104]. The study will include 1218 patients with high- and very-high-risk groups after radical or partial nephrectomy. The primary end point is DFS, with OS, toxicity and translational studies as secondary end points;

- The PROTECT trial is a double-blind, randomized, multicenter study comparing treatment with pazopanib for 1 year versus placebo [105]. The study will include 1500 patients with localized or locally advanced RCC after nephrectomy. The primary end point is DFS, with OS, safety, health outcome and quality of life as secondary end points;

- The ARISER trial (completed analysis is expected) studied cG250 (WX-G250; an immunoglobulin G1 antibody targeting carbonic anhydrase IX) in a multicenter, randomized, placebo-controlled, Phase III trial in clear cell RCC patients following complete or partial surgical removal of the affected kidney, in patients with no detectable metastases [106]. Carbonic anhydrase IX is a HIF downstream target gene that is expressed in all clear cell RCC, but is not detected in normal kidney or most other normal tissues [46]. It may be involved in cell proliferation and transformation.

Results from the above adjuvant trials will also be important to answer concerns emerging from laboratory reports that manipulation of the HIF and VEGF pathways either genetically or using angiogenesis inhibitors may potentially accelerate metastasis [47]. Studies using pancreatic neuroendocrine and glioblastoma multiforme tumor cells have shown that resistance to angiogenesis inhibitors may occur via a process of evasive resistance. Resistant clones develop using alternative proangiogenic pathways such as the FGF pathway and have been shown to be more invasive and demonstrate increased dissemination compared with tumor cells not treated with angiogenesis inhibitors [47]. This is therefore a concern for adjuvant studies if treatment resulted in recurrence of disease with tumor cells demonstrating a more aggressive phenotype.

What lessons have been learned so far?

Studies carried out to date have shown that the use of targeted therapies in the adjuvant setting presents a different set of challenges from their use in the metastatic setting. It is well known that the TKIs are associated with a number of common toxicities. Common to all currently used TKIs is that they are multitargeted agents, inhibiting a number of receptor kinases, including PDGFR-α and -β, stem cell factor receptor (KIT), RET and FMS-like tyrosine kinase-3 (Flt-3), in addition to VEGF receptors, with varying potency [48]. This
<table>
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CTD: Clinical Trials Database (see ClinicalTrial website [107]); DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; NCI: National Cancer Institute; NCIC: National Cancer Institute of Canada; OS: Overall survival; QoL: Quality of life; SWOG: Southwest Oncology Group.
lack of specificity brings with it a number of common side effects, often termed ‘off-target’ effects, including hypothyroidism, hand–foot syndrome, diarrhea, stomatitis and anorexia. Others, such as hypertension and lethargy, may in fact represent ‘on-target’ toxicities. In the metastatic setting, many patients require dose reductions (or stop therapy altogether), which has been shown to negatively impact on both quality of life and survival [49].

Unsurprisingly, toxicities have been shown to be particularly relevant to use of TKIs in the adjuvant setting. However, early data from adjuvant trials have demonstrated that the toxicity profile may be different than that observed during treatment in the metastatic setting with an often higher drop-out rate than expected but lower event rate than in standard practice [Eisen T, Pers. Comm.]. For example, toxicities in the SORCE trial have been higher than predicted with 35% of patients experiencing significant toxicities over the whole course of the trial, compared with a predicted rate of 20% [102]. Importantly, such toxicities have caused patients to drop out of adjuvant trials with the majority of drop-outs occurring within the first 12 weeks of treatment. Both the SORCE and ASSURE trials have had to increase enrollment targets to account for these drop-out rates (e.g., from 1332 to 1923 in the case of the ASSURE trial).

Interestingly, long-term toxicity has been less of a problem and actions have been taken to respond to early toxicity concerns in the first 3 months: both the SORCE and ASSURE trials have introduced half-dose lead-in periods with an emphasized dose-modification schedule with early prophylactic measures advised (see the ClinicalTrial website [107] for details). The aim of the first 12 weeks has also been modified such that the focus during this period is to identify a dose that the patient can tolerate well, rather than achieving the maximum dose. There has also been a realization that dose interruption early is helpful to ensuring that patients remain on treatment. This has since had a positive impact on drop-out rates [Eisen T, Pers. Comm.]. Since adjuvant studies take a considerable length of time to run, given the low event rate in this setting, it is especially important to respond to concerns and address issues quickly to ensure results are meaningful and relevant.

Equally, since the role of angiogenesis is less well understood in the earlier stages of RCC compared with the metastatic setting, it is difficult to predict whether targeted agents will be similarly effective in patients with no evidence of remaining disease after surgery. Therefore, patient selection is an important issue. To date, the studies in the adjuvant setting are focused on patients with intermediate- or high-risk disease, based mainly on factors such as stage, size and grade. Currently, no biomarker is available that predicts the effectiveness of angiogenesis inhibitors in RCC patients. However, several markers are being developed to tailor antiangiogenic therapy, although none have been validated in large, prospective trials [50,51]. Such a biomarker would be very helpful to identify and select those patients most likely to benefit from adjuvant treatments but also to spare patients potentially distressing toxicities when they would be unlikely to benefit.

Likewise, relevant biologic end points of therapy and progression remain elusive in RCC treatment. Therefore, an important aspect of all adjuvant trials is the correlative science that attempts to identify such markers. Yuasa et al. have recently reviewed the role of biomarkers in predicting the response to sunitinib treatment in the metastatic setting [52]. In addition to clinical factors, as defined by the Memorial Sloan–Kettering Cancer Center (MSKCC) score, genetic factors affecting the pharmacodynamics of sunitinib (e.g., the activity of drug efflux pumps and metabolizing enzymes), in addition to the baseline activity of the targeted pathway within each patient, have been shown to affect the response to sunitinib. Selection of appropriate biomarkers is therefore critical, especially within the adjuvant setting. The following factors have been included in the adjuvant trials described above: functional status of the tumor vasculature and markers of tissue angiogenesis and apoptosis and associated markers (e.g., immunohistochemistry for microvesSEL density and apoptosis); pharmacokinetics and genotyping (measurement of circulating proangiogenic markers and cells, drug levels, CYP3A4/5, B-RAF and VEGF polymorphisms); and proteomics on plasma and serum and hypermethylation markers (P16, VHL and others in urine and tumor tissue). The results will be essential to enable appropriate patient selection and to guide therapy with the aim of personalizing treatment to each individual patient. The ability to enrich trials for an
appropriate treatment population would also reduce cost and likely save time, particularly in the adjuvant setting.

How can clinical trials of adjuvant treatment in RCC be improved? Despite the availability of multiple treatment options, many questions and challenges remain for clinical trials of adjuvant treatment in RCC. In effect, these include optimal sequencing of the available agents (which is the best first-line or subsequent therapy for a given patient) in addition to how to design trials with appropriate comparison arms and end points, and ensure that well-tolerated and effective drug combinations are identified (including those in different classes and with different modes of action, such as targeted agents, cytotoxic agents and immunotherapy). Ongoing trials may answer some of these questions but many agents and combinations remain untested and are awaiting trials. Additionally, the current trials do not address the question of whether further risk stratification is needed, with high-risk patients receiving early postoperative therapy whereas medium-risk patients may be able to delay treatment.

The traditional approach to clinical trial design is to test each agent one by one in separate controlled trials. An alternative is the multiarm multistage (MAMS) trial design whereby several novel treatments are compared. The two approaches are compared in Figure 2. In the MAMS trial design, single-agent, single-arm Phase II trials are followed by a single MAMS trial of all combination therapies. For example, using current standard trial protocols, new agents (T1, T2 and T3) would be tested initially in three separate single-agent, single-arm Phase II trials, followed by three single-arm combination Phase II trials. The MAMS design rolls the Phase II assessment of the activity of combination therapy into the same trial as the Phase III assessment of effectiveness. The MAMS model therefore would require 1300 patients compared with 2100 patients with the traditional model (a saving of 800 patients).

MAMS trials therefore require fewer patients and less overall time, since patients are randomized from the start and different agents are tested concurrently rather than sequentially. There is also a shared control group and, at interim analyses, arms may be dropped if evidence so far suggests that they are unlikely to be effective (futility), or if sufficient evidence of effectiveness has been found already (efficacy). There is also no delay between Phase II and III assessments and MAMS trials require fewer applications for finance and approvals (one protocol, one grant application, one clinical trial agreement submission [per country], one ethics application [per country] and one research and development approval [per site]). Importantly, the trials infrastructure remains in place for a series of clinical questions and does not have to be rebuilt each time. Therefore, MAMS trials are more efficient and cheaper. An additional advantage for adjuvant trials in RCC patients is that more treatments can be tested with a limited set of patients (e.g., in different subtypes of RCC). MAMS trials are also more popular among patients as they stand a greater chance of being allocated to a new treatment.

However, the MAMS trial design also has some drawbacks, including the need for cooperation between different commercial companies, which

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**Figure 2.** Comparison of traditional and multiarm multistage clinical trial design. MAMS trial designs require fewer patients for control arms and have multiple points of analyses and can therefore be completed sooner.

C: Control/placebo; MAMS: Multiarm multistage; P: Point of primary analysis; S: Point of secondary analysis; T: Treatment/drug to be tested.
could cause significant delays in set-up time for trials if not addressed. For example, a trial involving those agents currently being tested in the adjuvant setting would require cooperation between four major pharmaceutical companies (Pfizer, Bayer, GlaxoSmithKline and Novartis). This problem has recently been addressed by the NIH’s National Center for Addressing Translational Sciences (NCATS) in the development of a collaborative program that will match researchers with a selection of pharmaceutical industry compounds to help scientists explore new treatments for patients. The pilot program incorporates innovative template agreements designed to streamline the legal and administrative process for participation by multiple organizations. These template agreements aim to reduce time, cost and effort, as well as allow greater participation than traditional partnerships, and may be helpful in the context of a MAMS trial design.

An additional issue that could potentially delay a MAMS trial is that the trial could not start until several agents are available. In renal cancer, there are currently several agents for which it would be useful to conduct a head-to-head trial within the adjuvant setting, including sunitinib/sorafenib, pazopanib, axitinib and everolimus; only the ASSURE trial will answer which of sunitinib or sorafenib may be more effective in the adjuvant setting. The MAMS trial design also allows for the addition of extra arms at later dates to respond quickly to new agents becoming available.

This trial design has been used in the STAMPEDE trial to compare hormone therapy alone with a combination of hormone therapy and either zoledronic acid, docetaxel (or both), celecoxib or abiraterone in prostate cancer [54,55]. The trial aims to recruit 4000 men with advanced prostate cancer between September 2005 and December 2013. It has recruited well and appears to be on-track to determine which, if any, therapy is beneficial for use in this setting. Importantly, when the trial came to its second planned intermediate activity analysis (a predetermined point at which sufficient data had been accrued to allow an intermediate analysis to take place) the STAMPEDE Trial Steering Committee decided that recruitment should be stopped to the celecoxib-containing trial arms due to a lack of sufficient benefit. Recruitment to the other arms continued unchanged as these passed the prespecified intermediate hurdle for activity. Since the possibility of stopping recruitment to arms is an integral part of the trial’s design and is built into the approved protocol, this did not constitute a substantial amendment and was initiated straight away. Additionally, a new arm was later added comparing abiraterone/prednisolone to control after abiraterone received marketing authorization in the USA and in the EU from September 2011 [56]. The STAMPEDE trial has therefore demonstrated that the MAMS approach is a practical as well as a theoretical advance.

Conclusion
There is a need for adjuvant treatment in RCC to reduce relapse rates. Significant Phase III trials on the adjuvant use of targeted therapy in RCC are ongoing. They investigate those therapies that have shown benefit in the treatment of metastatic RCC. Already, these trials have identified the need to respond to concerns and to address issues quickly to ensure results are meaningful and relevant in this setting. Significant challenges remain, particularly in the area of clinical trial design and the need to assess multiple potential therapies in a time- and cost-efficient manner, and to identify which patients are likely to benefit from adjuvant therapy. We suggest the MAMS trial design as a possible model to address these problems. The next few years will see reports on a number of adjuvant trials and therefore offer the promise of better outcome from RCC after surgical treatment.

Future perspective
Within the next 5–10 years, the role of adjuvant therapy for renal cancer will have been clarified. Important questions regarding which, if any, of the receptor TKIs (or the mTOR inhibitor everolimus) leads to improved outcomes for renal cancer patients will have been answered by the ongoing large clinical trials. Importantly, the tolerability of these agents within the adjuvant setting will have been assessed, which will allow clinicians to guide development of future therapies with improved knowledge regarding the level of acceptable toxicity in this patient group. Questions regarding scheduling of adjuvant therapy are also expected to be answered, including whether treatment can be delayed in medium-risk patients compared with those identified to have higher-risk disease. Increased use of imaging
and biomarkers capable of accurately assessing clinical response will allow clinicians to more accurately identify those patients most likely to benefit from treatment, while sparing those likely to have poor outcomes or those likely to suffer from intolerable treatment-related side effects.

Given the likely ongoing need to quickly and cost-effectively translate potential therapies from preclinical and early clinical studies into the clinical setting, assessment methods of clinical efficacy will need to become more streamlined. The MAMS clinical trial model is proposed by the authors as a potential strategy. Collaborations between different institutions, pharmaceutical companies and academic research institutions will need to evolve to achieve these goals. However, the future of adjuvant treatment in renal cancer remains an exciting area and the next 10 years will see key questions answered in the field.

Financial & competing interests disclosure
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References
Papers of special note have been highlighted as:
- of interest
- of considerable interest

10 First to describe the UCLA integrated scoring system to predict risk of relapse after surgery in renal cell carcinoma (RCC) patients.
12 Forms the basis for development of the Leibovich score used in some of the ongoing adjuvant trials.
Constitutive activation of hypoxia-inducible factors related to overexpression of hypoxia-inducible factor-1α in clear cell renal carcinomas. Cancer Res. 61, 5215–5222 (2001).


Useful review of current and future targeted therapies in RCC.


Good review and explanation of the multiarm multistage (MAMS) trial design.


**Websites**

5. A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma (RCC) (PROTECT). http://clinicaltrials.gov/ct2/show/NCT01235962