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Is there a role for adjuvant therapy after surgery in "high risk for recurrence" kidney cancer? An update on current concepts

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ABSTRACT

Background Although surgical resection remains the standard of care for localized kidney cancers, a significant proportion of patients experience systemic recurrence after surgery and hence might benefit from effective adjuvant therapy. So far, several treatment options have been evaluated in adjuvant clinical trials, but only a few have provided promising results. Nevertheless, with the recent development of targeted therapy and immunomodulatory therapy, a series of clinical trials are in progress to evaluate the potential of those novel agents in the adjuvant setting. In this paper, we provide a narrative review of the progress in this field, and we summarize the results from recent adjuvant trials that have been completed.

Methods A literature search was conducted. The primary search strategy at the MEDLINE, Cochrane reviews, and http://ClinicalTrials.gov/ databases included the keywords "adjuvant therapy," "renal cell carcinoma," and "targeted therapy or/and immunotherapy."

Conclusions Data from the S-TRAC study indicated that, in the "highest risk for recurrence" patient population, disease-free survival was increased with the use of adjuvant sunitinib compared with placebo. The ASSURE trial showed no benefit for adjuvant sunitinib or sorafenib in the "intermediate- to high-risk" patient population. The ARISER (adjuvant girentuximab) and PROTECT (adjuvant pazopanib) trials indicated no survival benefit, but subgroup analyses in both trials recommended further investigation. The inconsistency in some of the current results can be attributed to a variety of factors pertaining to the lack of standardization across the trials. Nevertheless, patients in the "high risk of recurrence" category after surgery for their disease would benefit from a discussion about the potential benefits of adjuvant treatment and enrolment in ongoing adjuvant trials.

Key Words Adjuvant therapy, renal cell carcinoma

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INTRODUCTION

Every year, approximately 338,000 people are diagnosed with kidney cancer globally, representing about 2.4% of the total cancer burden[1]. Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney cancers—affecting an estimated 300,000 people each year[2,3]. Approximately 30% of kidney cancer patients present with advanced or metastatic disease stage at diagnosis, with an average 5-year survival rate of approximately 11.7%[4,5].

The management of RCC, regardless of its histologic subtype or stage, involves surgical resection of the tumour through either a radical or partial nephrectomy[6]. Surgery is not usually curative in most cases of metastatic RCC (mRCC), but in a small proportion of patients, cytoreductive nephrectomy and metastasectomy might be curative[6]. In cases of localized RCC, surgical intervention is considered the optimal standard of care[6,7]. Nevertheless, postsurgical cancer recurrence is a prevalent issue in localized RCC (stage II or III disease), with a 5-year relapse rate of 30%–40%, and surgery is therefore insufficient for long-term disease-free survival (DFS)[8,9]. Hence, even though the current standard for postoperative care continues to be radiographic surveillance, the need for effective adjuvant therapy for localized "high risk for recurrence" RCC is an unmet need and a desire in the surgical community[8–10].

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Since the late 1990s, various agents have been tested in RCC in the adjuvant setting, most of which have yielded negative results[9–11]. Clinical trials with nonspecific immunotherapy agents have shown those agents to be ineffective for RCC in the adjuvant setting[12–19]. Similarly, trials with therapeutic vaccines, hormonal treatments, and radiotherapy have not demonstrated any benefit as adjuvant therapy in patients with RCC[20–30]. However, since about 2010, targeted therapy agents have become standard in the overall management of MRCC[7,31,32]. This new class of inhibitors specifically targets cellular processes that are critical for cancer progression. Apart from those agents, the recent emergence of targeted immunotherapy has also led to several investigations and advances in the MRCC treatment landscape[31,32]. However, the role of the foregoing agents in the adjuvant setting is not well understood, and hence the studies investigating their efficacy as adjuvant treatment have grown rapidly in number.

In the first segment of this narrative review, we provide an overview of targeted therapy and its recent transposition to the adjuvant setting in the context of RCC, and we outline the major adjuvant clinical trials that are currently evaluating the efficacy of various targeted therapy agents. Subsequently, we summarize the efficacy results for girentuximab, sunitinib, sorafenib, and pazopanib from the ARISER, ASSURE, S-TRAC, and PROTECT trials respectively, and we discuss the limitations in current adjuvant trial design. Finally, we review the current progress of immunomodulatory therapy in both the metastatic and adjuvant settings, and we highlight the future directions for research into adjuvant therapy.

TARGETED THERAPY

Systemic therapy for MRCC in particular has changed in recent years with the introduction of targeted therapy and the evolution of tyrosine kinase inhibitors (TKIs)[7,32–36]. Those developments have resulted directly from an improved understanding of the pathogenesis and molecular biology of RCC[31–36]. The novel therapeutic approach of TKIs provides better management of RCC pathology through the inhibition of targets such as the MTOR (mechanistic target of rapamycin) pathway and the vascular endothelial growth factor receptor, consequently helping to inhibit processes that are critical for cancer progression[7,32–36]. Particularly in cases of MRCC, those inhibitors (compared with the previously used immunotherapy and chemotherapy agents) have been effective in increasing rates of overall survival (OS) and response[7,32–36].

Seven drugs are now approved for targeted therapy, and several others are being evaluated in clinical trials[33–37]. At the molecular level, those drugs act by interrupting the molecular signal transduction of various signalling pathways, ultimately affecting pathogenic factors such as tumour vascularity, growth, and progression[33–37]. Sunitinib and pazopanib are currently the accepted standard of care for the management of MRCC, and because of their robust clinical efficacy and established toxicity profiles, they are the most widely used first-line agents[33–37]. As indicated by the COMPARZ trial, those two TKI drugs have been shown to have comparable efficacy with respect to progression-free survival, but different toxicity profiles, in the management of MRCC[38], exploiting the Von Hippel–Lindau (VHL) and hypoxia-inducible factor (HIF) pathway associated with clear cell RCC pathogenesis[39,40].

The VHL/HIF Pathway

Clear cell RCC normally entails a biallelic inactivation of the *VHL* tumour suppressor gene at the 3p25–26 locus[39,40]. Inactivation of *VHL* because of mutation, hypermethylation, or deletions results in the formation of defective PVHL protein—ultimately leading to the activation and upregulation of HIF[39,40]. Activated HIF protein serves as a transcription factor for various pro-tumorigenic target genes such as vascular endothelial growth factor, transforming growth factor α, and platelet-derived growth factor that are involved in pathogenic processes such as angiogenesis, tumour-cell proliferation, and cell survival[39,40]. Apart from that central pathway, the MTOR pathway intersects with the HIF pathway upstream of the *VHL* gene. Hence, that pathway also plays a critical role in influencing HIF process and function[39,40]. Inhibiting various targets in that pathway has yielded favourable results in MRCC patients[32–39].

Given the success of targeted therapy agents in the metastatic setting, recent efforts have focused on translating that success in the context of adjuvant therapy—the goal of which is to eliminate residual local micrometastatic disease[41,42]. However, the biologic plausibility of particular targeted therapies (that is, antiangiogenic agents) effectively treating local micrometastatic disease is debatable: unlike metastatic disease, micrometastatic disease might rely little on neoangiogenesis for viability[42]. Nevertheless, several trials have been initiated to investigate the effectiveness of targeted therapy in the adjuvant setting[41].

Clinical Trials

The contemporary endeavors to transpose targeted therapy into the adjuvant setting have been inspired by the increased clinical knowledge gained through the development and evaluation of interventions for stage IV disease[9–11,41]. Currently, several multicentre double-blind placebo-controlled randomized adjuvant clinical trials involving targeted therapy agents are underway[9–11,41–47]. Five involve TKIs; one involves an MTOR inhibitor; and one is investigating a monoclonal chimeric antibody (Table I). So far, four of the trials—ARISER, ASSURE, S-TRAC, and PROTECT—have been completed[43–47]; the others are still in progress.

ARISER Trial

The ARISER trial[43], completed in 2014, evaluated the efficacy of girentuximab, a monoclonal antibody to carbonic anhydrase IX (a HIF downstream target gene), in the adjuvant setting for patients at intermediate-to-high risk for recurrence. This multicentre phase III trial involved 864 patients with resected clear cell tumours who were randomized to receive either girentuximab or placebo once weekly for 24 weeks (summarized in Figure 1). Girentuximab was administered in a 50 mg dose during the first week, followed by a weekly dose of 20 mg for the next 23 weeks. The median DFS duration for participants in the intervention arm was 71.4 months [hazard ratio (HR): 0.97; 95% confidence interval

TABLE I Clinical trials of adjuvant targeted therapy that have either been completed or are in progress

Trial name	ClinicalTrials.gov ID	Intervention	Sample size	Inclusion criteria	Primary endpoint	Completion date
ARISER	NCT00087022	Girentuximab	864	Clear cell RCC T1b, N0, Nx, M0 or T2, N0, Nx, M0 Grade ≥ 3 Intermediate- to high-risk	DFS, OS	2014
ASSURE	NCT00326898	Sorafenib or sunitinib	1943	Any histology pT1bN0M0 (grades 3–4) pT2–4N1–3M0 Intermediate- to high-risk	DFS	2016
S-TRAC	NCT00375674	Sunitinib	615	Clear cell RCC pT2N0M0 (grades 3–4) or pT3–4N0M0 or pTxN1M0 High-risk	DFS	2016
PROTECT	NCT01235962	Pazopanib	1500	Clear cell RCC pT2N0M0 (grades 3–4) or pT3–4N0M0 or pTxN1M0 Intermediate- to high-risk	DFS	2017
SORCE	NCT00492258	Soraefenib	1420	Any histology pT1aN0M0 (grade 4), pT1bN0M0 (grades 3–4), pT2–4N0M0, pT1b-4N1M Intermediate- to high-risk	DFS	2019
ATLAS	NCT01599754	Axitinib	592	Clear cell RCC pT2–4N0M0 or pTxN1M0 High-risk	DFS	2019
EVEREST	NCT01120249	Everolimus	1218	Any histology pT1bN0M0 (grades 3–4) or pT2–4N1–3M0 Intermediate- to high-risk	DFS	2021

RCC = renal cell carcinoma; DFS = disease-free survival; OS = overall survival.

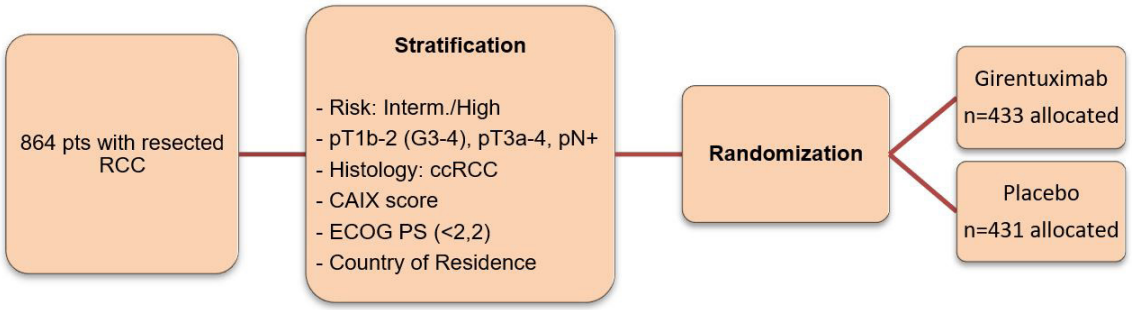

FIGURE 1 ARISER trial. RCC = renal cell carcinoma; ccRCC = clear cell RCC; CAIX = carbonic anhydrase IX expression; ECOG PS = Eastern Cooperative Oncology Group performance status.

(CI): 0.79 to 1.18], while the endpoint was never reached for the placebo group. The study therefore indicated no interventional advantage, but it recommended further investigation of adjuvant girentuximab in patients with high levels of carbonic anhydrase IX in affected renal tissue.

ASSURE Trial

The ASSURE trial[44], completed in 2016, was a randomized double-blind placebo-controlled phase III clinical trial in which 1943 intermediate- to high-risk patients from 226 study centres in North America were assigned to one of three intervention arms: sunitinib, sorafenib, or placebo (summarized in Figure 2). Sunitinib was administered at 50 mg for 54 weeks during 4 weeks of a 6-week cycle (the dose was revised to 25–37.5 mg because of toxicity). Sorafenib was administered at 400 mg twice daily throughout each cycle. Placebo administration was randomly assigned to be used either on the sunitinib schedule or the sorafenib schedule. The interventions were evaluated using DFS as the primary endpoint.

Trial results indicated that the median DFS duration was approximately 5.8 years for sunitinib (HR: 1.02; 97.5% CI: 0.85 to 1.23; $p = 0.8038$), 6.1 years for sorafenib (HR: 0.97; 97.5% CI: 0.80 to 1.17; $p = 0.7184$), and 6.6 years for placebo—hence suggesting no survival benefit from the interventions relative to the placebo. Instead, further detrimental effects because of the increased toxicity of the treatment (despite the dose reductions) were reported—suggesting no benefit of these particular TKIs in the adjuvant setting. Notably, this trial had a higher number of TKI dose reductions (potentially suggesting suboptimal drug dosing) and included more "intermediate risk for recurrence" patients than did other trials.

S-TRAC Trial

The prospective randomized double-blind phase III S-TRAC study[45,46] was also completed in 2016. Of the 615 patients from 21 countries who underwent randomization, 309 were assigned to the sunitinib arm, and 306, to the placebo arm (summarized in Figure 3). These patients were all at high risk for recurrence. Sunitinib was administered at 50 mg for 1 year during 4 weeks of a 6-week cycle. The interventions were evaluated by comparing DFS, the primary endpoint of the study, between the two trial arms.

The study results indicated that the median DFS duration was 6.8 years (95% CI: 5.8 years to not reached) in the sunitinib group and 5.6 years (95% CI: 3.8 years to 6.6 years) in the placebo group (HR: 0.76; 95% CI: 0.59 to 0.98; $p = 0.03$). The adverse effects observed in sunitinib recipients were consistent with the known toxicity profile for that agent. The primary results from the trial therefore support the potential for sunitinib to be a treatment option in the adjuvant setting, with a DFS advantage for patients at high risk. Those results have been further supported by subgroup analyses. However, mature OS data have not yet been reported. Based on the results currently reported from the trial, sunitinib was recently approved for adjuvant therapy by the U.S. Food and Drug Administration, making it the first adjuvant treatment approved for RCC. Approval in Canada for sunitinib as adjuvant therapy is under Health Canada review.

PROTECT Trial

The PROTECT study[47], completed in 2017, was a phase III randomized clinical trial that evaluated the efficacy of adjuvant pazopanib (compared with placebo) in preventing RCC recurrence in patients at intermediate-to-high risk (summarized in Figure 4). The trial enrolled 1538 patients, and most of those given pazopanib received a revised dose of 600 mg daily for 1 year (a reduction from 800 mg, a dose that caused severe side effects). The interventions were evaluated by comparing DFS in the two trial arms as the primary endpoint.

The study did not meet its primary endpoint and indicated no significant benefit of pazopanib 600 mg, compared with placebo, in prolonging DFS (HR: 0.86; 95% CI: 0.70 to 1.06; $p = 0.165$). However, a subgroup analysis of patients who received pazopanib 800 mg indicated a 31% decline in DFS (HR: 0.69; 95% CI: 0.51 to 0.94; $p = 0.02$). Although conflicting DFS results were observed in the 600 mg and

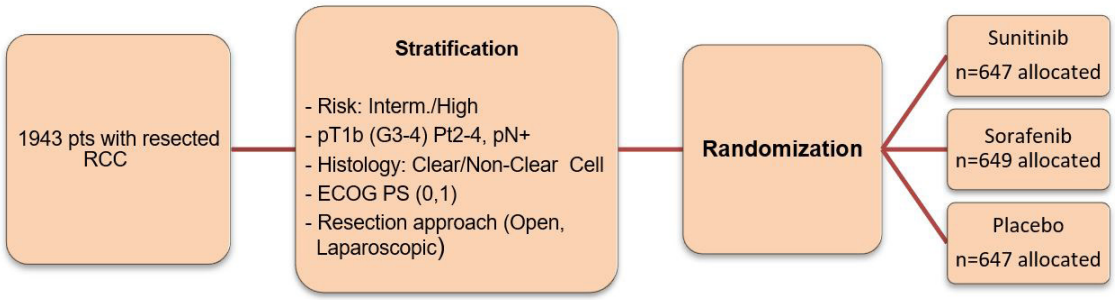

FIGURE 2 ASSURE trial. RCC = renal cell carcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status.

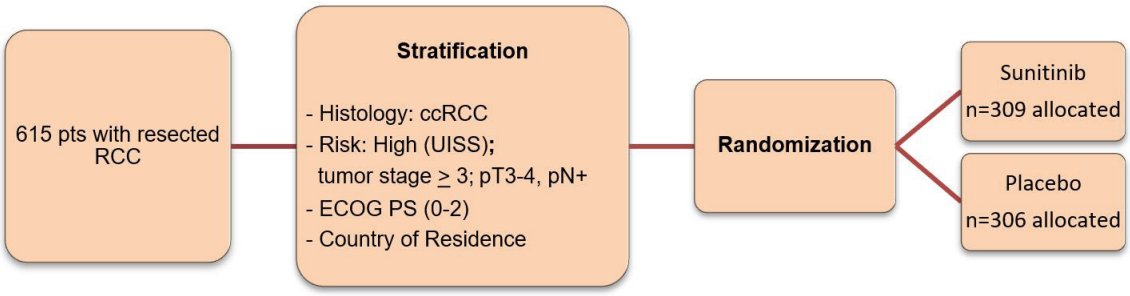

FIGURE 3 S-TRAC trial. RCC = renal cell carcinoma; ccRCC = clear cell RCC; UISS = University of California–Los Angeles integrated staging system; ECOG PS = Eastern Cooperative Oncology Group performance status.

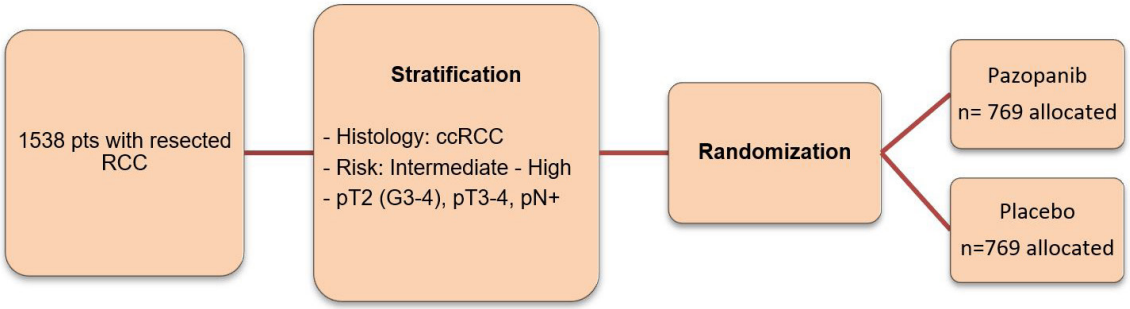

FIGURE 4 PROTECT trial. RCC = renal cell carcinoma; ccRCC = clear cell RCC.

800 mg groups, the study reported similar adverse event profiles in both groups.

Comparing Current Adjuvant Trial Designs

The distinct sample groups, dose regimens, risk assessment criteria, and trial methods used in the current set of completed trials might account for the differing outcomes reported[43–47]. Collectively, those differences represent a fundamental limitation affecting all current adjuvant clinical trials.

First, the patient inclusion criteria characteristically vary, in multiple ways, in all the trials[43–47]. For example, in S-TRAC, the selected sample exclusively included patients with late-stage (high risk) locoregional clear cell RCC; other trials such as ASSURE, ARISER, and PROTECT used less-restrictive criteria and included patients with stage I or stage II tumours and non–clear cell histologies[43–47]. In addition, because of toxicity, the starting dose for patients in the ASSURE and PROTECT trials was reduced (compared with the dose in S-TRAC) to suboptimal levels[44–47]. That variability in the dose regimen could have affected the results, as indicated by the increased treatment efficacy seen in S-TRAC compared with ASSURE and for pazopanib 800 mg compared with 600 mg in PROTECT[44–47]. Another major cause of heterogeneity lies in the risk assessment and stratification criteria, given that the scoring systems used in the current set of adjuvant trials were not standardized, invariably contributing to a differential assessment of recurrence risk[43–47]. With respect to the conflicting sunitinib trials (S-TRAC vs. ASSURE), additional sources of variation that might have led to inconsistent outcomes include varied dose regimens [specifically, the variable midtrial dose reductions for sunitinib (ASSURE allowed dose reduction to as low as 25 mg daily; S-TRAC used 37.5 mg daily)], variability in compliance, variability in the data review process for endpoint assessment (independent central review in S-TRAC vs. blinded investigator review in ASSURE), and differing trial criteria for establishing disease status and assessing primary endpoint status[45,46,48].

And apart from the foregoing concerns, an underlying point of contention with respect to the overall design of adjuvant trials is whether DFS is the most appropriate endpoint in this context[49–51]. On the whole, from a testing and regulatory approval viewpoint, using DFS as a surrogate endpoint is arguably a faster, accessible, and more logistically feasible option for evaluating a treatment's effect on the disease process, hence allowing for accelerated approval by certain regulatory boards such as the U.S. Food and Drug Administration—especially if a positive correlation with survival has been established[51,52]. However, from a clinical perspective, it can be difficult to draw conclusions about the clinical benefit of adjuvant therapy without information about the treatment's ultimate effect on OS[49,50]. Within the context of nonmetastatic RCC, no intermediate clinical endpoint has currently been validated as an appropriate surrogate for OS[51]. A recent meta-analysis by Harshman *et al.*[51] looked at whether DFS can serve as an early clinical surrogate for OS in adjuvant trials for localized RCC and found only a modest correlation between the 5-year rates of DFS and OS ($R^2 = 0.48$), as well as between treatment effect derived using the HRS for DFS and OS ($R^2 = 0.44$). The merit of using DFS as an intermediate clinical endpoint for an adjuvant trial is therefore debatable, potentially making it difficult to recommend that all patients be considered for adjuvant therapy[49–52].

Stratifying Risk of Recurrence

A critical element in both the testing and effective clinical use of adjuvant therapy is determining whether the patient is at high risk of disease recurrence after nephrectomy and, accordingly, identifying the patients most likely to benefit from the therapy. As discussed earlier, no standard for the determination of recurrence risk is currently in use for testing adjuvant therapies.

Several models and clinical nomograms have been developed to predict the risk of disease recurrence and progression, as well as to evaluate additional oncologic endpoints[53–63]. Examples of validated models include the Cindolo Recurrence Risk Formula; the Karakiewicz nomogram; the Kattan nomogram; the Mayo Clinic SSIGN (stage, size, grade, and necrosis) scoring system; and the University of California–Los Angeles Integrated Staging System (UISS). For a relatively robust evaluation, these systems usually incorporate information relating to various prognostic signs and indictors such as tumour size, stage, and characteristics; clinical risk factors; and various other pathologic features and signs[53–64]. Of the available models, the UISS and the SSIGN scoring system have shown relatively better discriminative accuracy in some comparative studies and are the models most commonly used[60,61,65]. The

SSIGN scoring algorithm incorporates information about TNM stage, tumour size, nuclear grade, and presence of histologic necrosis. The UISS uses TNM stage, Fuhrman grade, and Eastern Cooperative Oncology Group performance status[57,58,60,61]. Both models have been externally validated in independent studies[66–68].

The UISS nomogram places recurrence risk into three broad categories: low, intermediate, and high risk[69]. That stratification provides a practical guideline for assessing and classifying risk in RCC patients, clinically differentiating patients with localized RCC based on probability of survival and disease recurrence (5-year recurrence-free rate—low risk, 90.4%; intermediate risk, 61.8%; high risk, 41.9%; 5-year survival rate—low risk, 92%; intermediate risk, 67%; high risk, 44%).

In clinical settings, patients can be stratified using an independent clinical assessment of various factors such as tumour stage and size, nuclear grade, and performance status[60,64,69,70]. Although the foregoing factors have not formally been validated as independent models for recurrence-risk prediction, they are important prognostic indicators for the various oncologic outcomes and endpoints that are invariably associated with the risk of disease relapse and overall disease-specific survival[63,64,71–74]. Among those prognostic factors, tumour stage is the most important for RCC patients, with pT1a, pT1b, pT2, pT3a, pT3b, pT3c, and pT4 tumours having 5-year cancer-specific survival rates of 97%, 87%, 71%, 53%, 44%, 37%, and 20% respectively[73]. An evaluation of those factors—particularly tumour stage—can therefore serve as a guide for a preliminary differentiation between high-, intermediate-, and low-risk categories in the clinical setting[69–74]. The correlation between some of those prognostic factors and recurrence risk has been supported by independent studies that have reported relatively higher recurrence rates for smaller, early-stage tumours and lower recurrence rates for larger, late-stage tumours[70–75]. Thus, patients with T1a–b (grade 1–2) tumours can be estimated to have a lower recurrence risk, and those with T3–4 tumours can be placed into the high-risk category[70–75]. Currently, with respect to those risk levels, patients who have the highest risk of disease recurrence can potentially benefit from adjuvant intervention after surgical resection of their tumour.

The incorporation of biotechnology and an improved understanding of genetic and molecular markers could potentially lead to the next major advancement in the prediction of relapse risk[75–78]. Recent studies have reported the development of novel gene assays and have elucidated several new biomarkers[75–78]. Nonetheless, further investigation, testing, and development are required before molecular approaches can be clinically applied in an efficient and economically viable manner.

TARGETED IMMUNOMODULATORY THERAPY

The development of therapy that targets oncogenic signalling pathways has advanced the treatment landscape for patients with advanced RCC. Nonspecific immunotherapy with interleukin 2 and interferon alfa had been the mainstay in the management of metastatic disease, but the advent of targeted therapy, which yielded relatively better response rates, caused a shift away from those agents[12–19,31–36]. However, in recent years, cancer immunotherapy has been revisited, and as a result, targeted immunomodulatory therapy with novel immunomodulating agents has been reincorporated into combination regimens for the management of MRCC—hence allowing for an induced immunologic effect in addition to an inhibitory effect on the biology and microenvironment of the tumour[79,80]. That approach has been inspired in part by resistance to standard targeted therapy that is progressively being manifested in the landscape of metastatic disease management[79,80].

Given that tumours use multiple mechanisms to evade and suppress the immune system, research aiming to generate a better understanding those mechanisms of immunomodulation has been critical in informing the therapeutic landscape[79,81]. In particular, an improved understanding of the factors regulating the antitumour immune response has led to the development of a novel form of cancer immunotherapy involving checkpoint inhibitors and other therapies such as T-cell agonists, adoptive T-cell therapies, and novel vaccines, all of which are being evaluated in various trials involving patients with MRCC[79,81].

Immune Checkpoint Inhibitors

Immune checkpoints serve a critical protective function, preventing an immune response against host cells through a series of complex interactions[81–83]. However, investigation into the pathogenic mechanisms of RCC revealed that cancer cells can induce similar interactions with host checkpoint receptors and can thus suppress the human immune response[81–83]. Immune checkpoint inhibitors counter those molecular mechanisms that tumour cells use to evade immune recognition[81–83].

The PD-1 and CTLA-4 proteins are currently the most well understood inhibitory checkpoint receptors[81–83]. The PD-1/PD-L1 axis involves an inhibitory interaction between a T-cell inhibitory ligand PD-L1, expressed on the surface of tumour cells, and a PD-1 receptor on the lymphocyte[81–83]. Mimicking that interaction ultimately allows tumour cells to evade the adaptive immune response by suppressing T-cell function. Tumour cells similarly exploit the CTLA-4 pathway[81–83]. During an adaptive immune response, immune activation occurs through an interaction between the T-cell receptor and the antigen-presenting cell, together with co-stimulation of CD28 on the T cell[81–83]. That activation is negatively regulated by an inhibitory interaction between CTLA-4 and its ligands, CD80 or CD86[81–83]. Thus, the inhibition of those checkpoint receptors in both pathways by targeted antibodies could allow for T-cell activation and effective immune function[81–83].

The first checkpoint inhibitor to demonstrate a survival benefit in patients with MRCC was nivolumab, an anti–PD-1 monoclonal antibody[84]. Nivolumab received U.S. Food and Drug Administration approval in 2015 based on the results from a trial comparing nivolumab with everolimus, which yielded positive response rates when nivolumab was used for the treatment of advanced RCC in patients who had undergone prior antiangiogenic therapy[84]. Multiple other checkpoint inhibitors are currently being evaluated in various trials for advanced RCC[81–83].

Immunomodulatory Therapy in the Adjuvant Setting

Given their recent development, many immune checkpoint inhibitors are still being evaluated for efficacy and toxicity in mRCC, and hence investigation of those agents in the adjuvant setting has been limited. Currently, a few ongoing clinical trials are evaluating checkpoint inhibitors in both the adjuvant and neoadjuvant (pre-surgery) settings (Table II).

The phase III IMmotion010, KEYNOTE-564, and CheckMate 914 trials are evaluating the efficacy and safety of, respectively, adjuvant atezolizumab, pembrolizumab, and nivolumab–ipilimumab (combination regimen) for the prolongation of DFS in patients with RCC who are at high risk of disease recurrence post-nephrectomy (see NCT03024996, NCT03142334, and NCT03138512 at http://ClinicalTrials.gov/). In addition to the adjuvant trials, the PROSPER trial (neoadjuvant setting) is evaluating the efficacy of pre-nephrectomy nivolumab (NCT03055013 at http://ClinicalTrials.gov/). Those trials are currently in their pre-recruitment or recruitment phases and are anticipated to be complete by 2022–2024.

Apart from the agents being investigated in the foregoing clinical studies, several other checkpoint inhibitors are in development and still others are currently being evaluated in trials for mRCC and are likely to be subsequently assessed in the adjuvant setting[81–83].

CONCLUSIONS AND FUTURE DIRECTIONS

Targeted therapy and immunotherapy have become the current mainstays in the management of mRCC, and the success of those agents in advanced-stage disease has been the driving force behind the increasing number of trials of targeted therapy in the adjuvant setting. The emergence of immune checkpoint inhibitors in recent years has further led to important advances in the understanding and management of mRCC. However, many ongoing trials have yet to be completed, and ample potential remains for further investigation—especially with respect to combination regimens. Unfortunately, the evidence that has emerged from this progress in the field currently remains incongruent. The adjuvant clinical trials completed so far (ARISER, PROTECT, S-TRAC, and ASSURE) have reported negative or conflicting results. Additional large-scale trials are still in progress. The existing trial designs have several limitations, with the key limitation being an overall lack of standardization in the assessment criteria.

Future directions include incorporating a genetic recurrence score to evaluate risk of relapse in patients with RCC, developing an adequate and an objectively standardized adjuvant trial design, identifying novel biomarkers, and evaluating novel drug targets. Based on results from current trials, the "high risk for recurrence" RCC patient population (T3–4, grades 3–4) might benefit from adjuvant sunitinib, which provides a DFS advantage, but no observed OS benefit to date. Patients in this category who are interested in adjuvant therapy would benefit from a discussion with their oncologist about the potential benefits and risks of adjuvant treatment after surgery for kidney cancer and about enrolment in adjuvant immuno-oncology trials that are currently recruiting.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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TABLE II Ongoing adjuvant and neoadjuvant clinical trials evaluating checkpoint inhibitors

Trial name	ClinicalTrials.gov ID	Intervention	Estimated enrolment	Primary endpoint	Start date	Completion date
PROSPER	NCT03055013	Nivolumab (pre-Nx)	766	DFS	2 Feb 2017	2022
KEYNOTE-564	NCT03142334	Pembrolizumab	950	DFS	9 Jun 2017	2022
CheckMate 914	NCT03138512	Nivolumab, ipilimumab	800	DFS	3 Jul 2017	2023
IMmotion010	NCT03024996	Atezolizumab	664	DFS	3 Jan 2017	2024

DFS = disease-free survival.

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