Provisional chapter

Current Role of Adjuvant Therapy in High Risk for Recurrence Resected Kidney Cancer

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Additional information is available at the end of the chapter

Abstract

Renal cell carcinoma accounts for about 2% of all adult malignancies. More than 300,000 individuals are affected each year. Unfortunately, around 30% of cases are discovered in advanced stages. Surgical resection remains the mainstay of treatment for localized disease and relapses can reach up to 40% in some cases. The effective treatment of metastatic RCC with systemic targeted therapy gives a strong rationale for its use as adjuvant treatment in high-risk patients. This chapter reviews different modalities that have been used as an adjuvant therapy for nonmetastatic renal cancer. Clinical trials using targeted therapy are discussed in detail, as they are becoming options for treatment in high-risk patients. While the current set of completed adjuvant clinical trials have provided conflicting results, there are additional large-scale trials that are still in progress. Future directions include—incorporating a genetic recurrence score to evaluate risk of relapse in patients, developing an adequate and an objective standardized adjuvant trial design, identifying novel biomarkers, and evaluating novel drug targets. Based upon current clinical trial evidence, motivated high-risk patients should have a discussion with the urology oncology team regarding the benefits of adjuvant TKI sunitinib or consider enrollment in current ongoing immuno-oncology (IO) adjuvant clinical trials.

Keywords: renal cell carcinoma, adjuvant treatment for RCC, treatment of high-risk RCC, targeted therapy as adjuvant

1. Introduction

Every year, approximately 338,000 individuals are diagnosed with kidney cancer globally, representing about 2% of all cancers [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 represent an advanced disease stage at diagnosis, with an average 5-year survival rate of approximately 16% [4, 5].

The management of RCC, regardless of its histological subtype or stage, involves surgical resection of the tumor through either a radical or partial nephrectomy [6]. While surgery is not curative in cases involving metastatic disease, with localized RCC, surgical intervention is considered the optimal standard of care [6, 7].

But despite that, postsurgical recurrence of cancer is a prevalent issue in cases of localized RCC (stage 2 or 3 disease) with a 5-year relapse rate of 30–40% and, as such, surgery is insufficient for long-term disease free survival [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 would be helpful and desired by the surgical community [8–10].

In view of these findings and the effective treatment of metastatic RCC with Immunotherapy in the 1990s or more recently with targeted therapy, a strong rationale for systemic adjuvant therapy exists in high risk for recurrence patients.

In this chapter, we review different treatment modalities have been used as an adjuvant therapy for nonmetastatic renal cancer postsurgical resection with emphasis on targeted therapy as becoming an option to offer patients.

2. Stratifying risk of recurrence

A critical element in both the testing and effective clinical use of adjuvant therapy involves determining whether there is a high risk of disease recurrence post nephrectomy and accordingly identifying patients that are most likely to benefit from the therapy. As discussed earlier, the determination of recurrence risk is currently nonstandardized in adjuvant therapy testing. Several models and clinical nomograms have been developed to predict the risk of disease recurrence and progression, as well as evaluate additional oncological endpoints [11–19]. Examples of some validated models include the Cindolo Recurrence Risk Formula, Leibovich scoring system, Karakiewicz scoring system, Kattan nomogram, Mayo Clinic stage, size, grade, and necrosis scoring system (SSIGN), and the University of California Los Angeles Integrated Staging System (UISS) [11–19] (**Tables 1** and **2**). These systems usually incorporate information regarding different variables and various prognostic signs and indictors such as tumor size, stage and characteristics, clinical risk factors, and various other pathological features and signs for a relatively robust evaluation [11–21]. Among these models, the UISS, Kattan and SSIGN nomograms have shown relatively better discriminative accuracy in some comparative studies and hence are most commonly utilized [13, 22, 23].

In terms of a general approximation, recurrence risk can be segregated into three broad categories based on the UISS nomogram: low, intermediate and high risk [18]. These three risk groups

Characteristics		Points
Tumor	pT1a	0
	pT1b	2
	pT2	3
	pT3-pT4	4
Dimension	<10 cm	0
	>10 cm	1
Fuhrman	1–2	0
	3	1
	4	3
Tumor necrosis	Absent	0
	Present	1
Lymph nodes	pNx/pN0	0
	pN1-pN2	2

Table 1. Leibovich prognosis score.

T stage	1				2	3				4
Furman grade	1–2		3–4		1–4	1		2–4		1–4
ECOG PS	0	>1	any	>1	any	0	>1	0	>1	any
Risk group	Low	Intermediate							High	

Table 2. UISS prognosis score.

are differentiated based on the probability of survival and disease recurrence and patients, in a clinical setting, can be stratified through an independent clinical assessment of UISS components, such as tumor stage, grade, and other pathophysiological characteristics [18, 19]. While the UISS components have not been formally validated as independent recurrence risk prediction models, they are important prognostic indicators for various oncological outcomes and endpoints that are invariably linked with the risk of disease relapse [18, 19]. As such, an evaluation of tumor characteristics—particularly tumor stage—can serve as a rough guide for preliminary differentiation between high, intermediate and low risk categories in the clinical setting. [24–27] This correlation has been supported by independent studies which have reported higher recurrence free survival (RFS) rates for smaller, T1a-T1b stage tumors and lower RFS rates for larger, T3-T4 stage tumors [24–27]. Thus, patients with T1a-T2a tumors can be estimated to have lower recurrence risk while those with T3b-T4 tumors can be placed into the high-risk category [24–27]. Among these varying risk levels, currently only those who present a high risk of disease recurrence can potentially benefit from adjuvant therapy postsurgical resection of the tumor.

The incorporation of biotechnology and an improved understanding of genetic and molecular markers may potentially lead to the next major advancement in improving the predictive accuracy of relapse risk. Recent studies have reported the development of novel gene assays

and have further elucidated several new biomarkers [28–31]. Nonetheless, further investigation, testing and development is required before molecular approaches can be incorporated for clinical application in an efficient and economically viable manner.

3. Immunotherapy IL2,IFα

Two trials that used adjuvant IFN-α [32, 33] and one study that used adjuvant high-dose IL-2 (82) were negative for any benefit. The latter study was designed and powered to show an improvement in predicted 2-year DFS from 40% for the observation group to 70% for the treatment group. Despite full accrual 30% improvement in 2-year DFS could not be achieved which lead to early study closure.

Combination treatment with IFN-α and IL2 also failed to improve DFS in one trial [34].

The combination of cytokines with 5-fluorouracil (5-FU) also failed to improve DFS in the adjuvant setting [35, 36].

In one randomized adjuvant trial, triple combination therapy using IL-2, IFN-α, and5-FU was associated with significant toxicity which leads to 35% of the patients did not complete the study and also resulted in no benefit in DFS or OS [37].

4. Tumor vaccines

Autologous irradiated tumor cells mixed with bacillus Calmette-Guérin (BCG) were tested in two randomized trials and did not result in prolonged DFS [38–40].

Similarly, autologous, tumor-derived heat-shock protein (glycoprotein 96)-peptide complex (HSPPC-96; vitespen) did not result in a statistically significant improvement of DFS [41].

A trial with an autologous renal tumor cell vaccine only reported improved DFS in the vaccine group [42], but the number of patients lost after the randomization step, the imbalance of this loss, and the absence of tabulation of OS led to criticism of the results [43].

This therapy has not been implemented in routine clinical practice.

5. Hormonal therapy

The occasional response of patients with metastatic RCC to hormonal therapy with medroxyprogestrone acetate (MPA) provided a rationale in trying it in adjuvant sitting.

In a prospective randomized trial of adjuvant MPA after radical nephrectomy, 136 patients received either MPA 500 g (three times a week) for 1 year or observation. With a median follow up of 5 years. There were no significant differences in relapses between the adjuvant group and the observation group (32.7 vs. 33.9%, respectively) [44].

6. Radiotherapy

Radiotherapy has been used for symptoms palliation in metastatic RCC like hematuria and painful bone metastasis. Also, long-term PFS has been reported for in a subset of patients following radiotherapy for solitary bone metastases [31].

One prospective, randomized study in 72 patients comparing administration of radiation of the kidney bed, and ipsilateral and contralateral lymph nodes for stages II and III RCC versus observation reported relapse rates of 48% in both groups. Forty-four percent of patients in the radiotherapy arm had significant complications that contributed to the death of 19% of patients [45–47].

7. Adjuvant therapy in the era of the new targeted therapy

7.1. Targeted therapy

Systemic therapy for mRCC has particularly changed over the last decade with the introduction of targeted therapy and the evolvement of tyrosine kinase inhibitors (TKI) [7, 49–53]. This development has directly resulted from an improved understanding of the pathogenesis and molecular biology of RCC [49–54]. TKIs have provided a novel therapeutic approach for better managing the pathology through the inhibition of targets such as the mammalian target of rapamycin (mTOR) pathway and the vascular endothelial growth factor receptor (VEGFR), which consequently help inhibit processes that are critical for cancer progression [7, 49–53]. Particularly in cases of metastatic RCC, these inhibitors have been effective in increasing the overall survival and response rates than previously used immunotherapy and chemotherapy agents [7, 49–53].

Seven drugs are now approved for targeted therapy, and several others are being evaluated in clinical trials [50–53, 55]. At the molecular level, the mechanism of these drugs involves interrupting the molecular signal transduction of various signaling pathways which then ultimately affects pathogenic factors like tumor vascularity, growth and progression [50–53, 55]. Sunitinib and Pazopanib are currently the accepted standard of care for the management of metastatic RCC and are the most widely used first line agent due to their robust clinical efficacy and established toxicity profile [50–53, 55]. The current set of therapeutic agents used in targeted therapy exploit the Von Hippel-Lindau (VHL) and hypoxia-inducible factor (HIF) pathway associated with clear cell RCC pathogenesis [56, 57].

7.2. VHL-HIF pathway

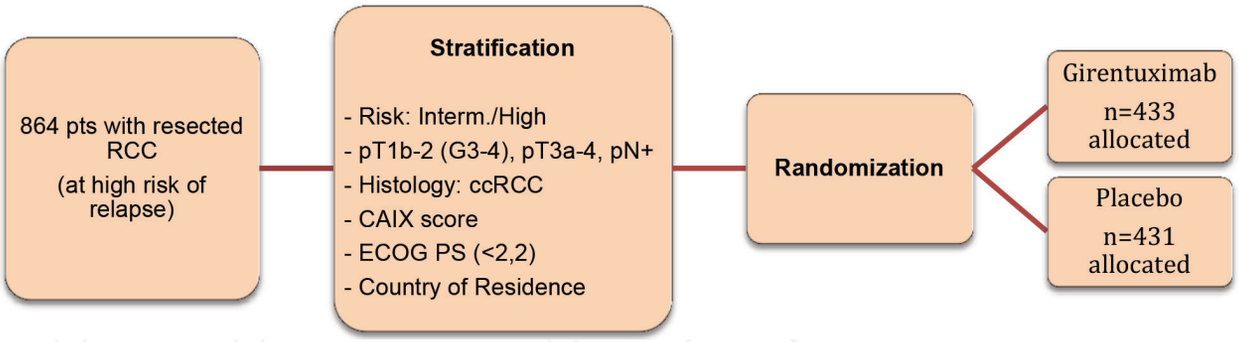
Clear Cell RCC (ccRCC) normally entails a biallelic inactivation of the VHL tumor suppressor gene at the 3p25-26 locus. VHL inactivation, which occurs due to factors such as mutation, hyper-methylation, or deletions, results in the formation of defective pVHL protein—ultimately leading to the activation and upregulation of HIF-1α [56, 57]. Activated HIF protein serves as a transcription factor for various pro-tumorigenic target genes such as vascular

endothelial growth factor (VEGF), transforming growth factor-α and platelet-derived growth factor (PDGF) that are involved in pathogenic processes like angiogenesis, tumor cell proliferation and cell survival. [56, 57] Apart from this central pathway, the mTOR pathway also intersects with HIF pathway upstream of the VHL gene and hence also plays a critical role in influencing HIF process and function. [56, 57] Thus, inhibiting different targets in this pathway has yielded favorable results in mRCC cases [50–53, 55–57]. Given the success of targeted therapy agents in the metastatic setting, recent efforts have been focused into translating this into the adjuvant setting.

7.3. Clinical trials: targeted therapy in adjuvant setting

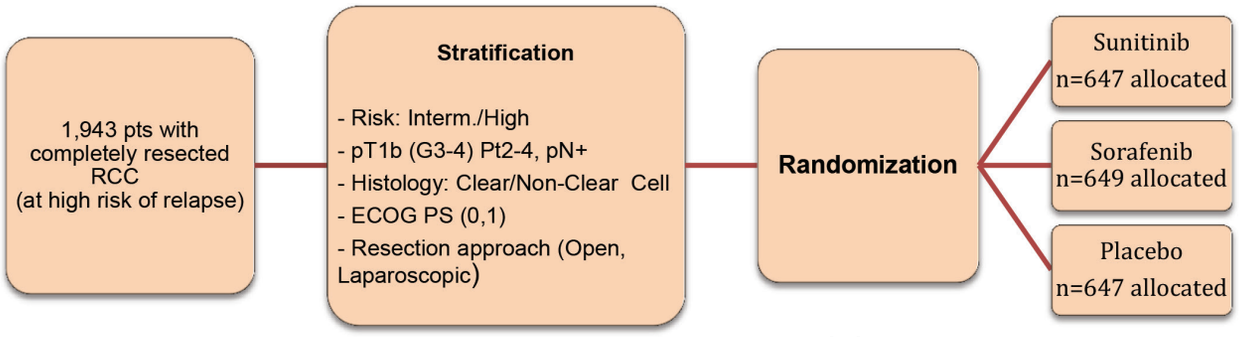
The contemporary endeavors to transpose targeted therapy in the adjuvant setting have been inspired by the increased clinical knowledge gained through the development and evaluation of interventions for stage IV disease [9, 10, 58, 59]. There are currently seven multicenter, double-blind, placebo-controlled, randomized adjuvant clinical trials, involving targeted therapy agents [9, 10, 58, 59]. Five of these trials involve tyrosine kinase inhibitors, while one involves an mTOR inhibitor and the other a monoclonal chimeric antibody [9, 10, 58–63]. So far, four of these trials have been completed including the, ARISER, ASSURE, S-TRAC and PROTECT trials while the other ones are still in progress [60–63].

7.3.1. ARISER trial



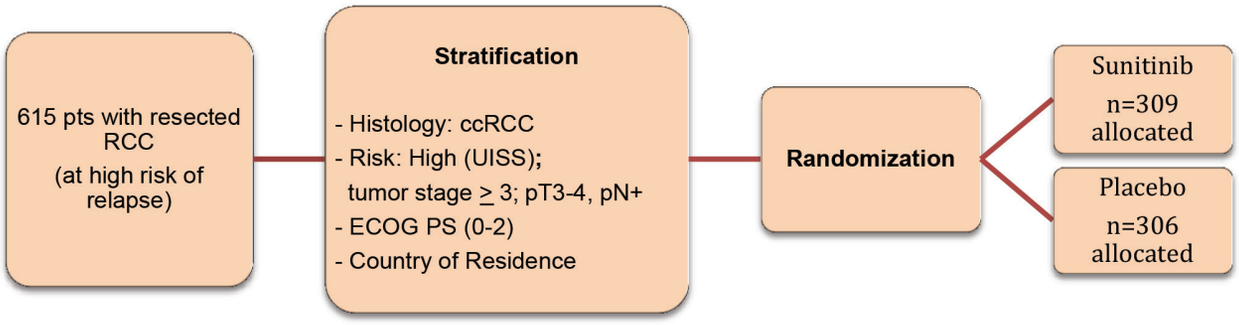
This ARISER trial, completed in 2014, evaluated the efficacy of girentuximab [60], a monoclonal antibody to carbonic anhydrase IX (a HIF downstream target gene), in the adjuvant setting for intermediate to high risk for recurrence patients. This multicenter, phase III trial involved 864 patients with resected clear cell tumors, who were randomized to receive either girentuximab or placebo, once a week, for 24 weeks. Girentuximab recipients received a 50 mg dose during the first week followed by a weekly dose of 20 mg for the next 23 weeks. The median disease free survival (DFS) duration for the participants in the intervention arm was 71.4 months (HR: 0.97; 95% CI, 0.79–1.18) while the endpoint was never reached for the placebo group. As such, the study indicated no interventional advantage but it recommended further investigation of adjuvant girentuximab in patients with high levels of CAIX in affected renal tissue.

7.3.2. ASSURE trial



The ASSURE trial, completed in 2016, was a randomized, double-blind, placebo-controlled, phase 3 clinical trial in which 1943 patients from 226 study centers in North America were assigned to one of three intervention arms—sunitinib, sorafenib or placebo in intermediate to high-risk patients [61]. Sunitinib patients received 50 mg for 54 weeks on a 4 of 6 week cycle; sorafenib recipients received 400 mg twice per day throughout each cycle, and placebo recipients were randomly assigned either the sunitinib placebo or the sorafenib placebo. 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: 0.85–1.23; P = 0.8038], 6.1 years for sorafenib (HR: 0.97; 97.5% CI: 0.80–1.17; P = 0.7184), and 6.6 years for placebo—hence suggesting no survival benefit from the interventions relative to the placebo. Instead, the results further reported detrimental effects due to the increased toxicity of the treatment despite the dose reductions—suggesting no benefit of the particular TKI in the adjuvant setting. Of note, this trial had a higher number of TKI dose reductions (potentially suggesting suboptimal drug dosing) and more intermediate risk for recurrence patients than other trials.

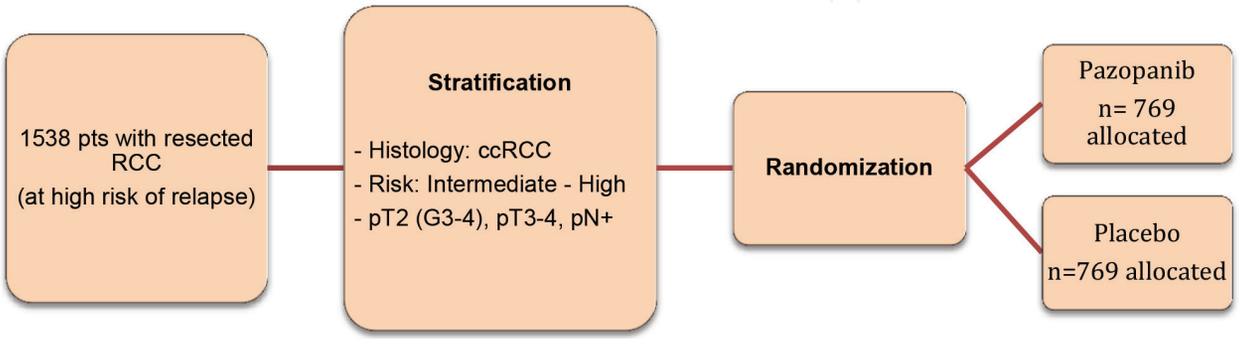
7.3.3. S-TRAC trial



The S-TRAC study, also completed in 2016, was a prospective, randomized, double-blind, phase 3 clinical trial involving 615 patients from 21 countries [62]. Of the 615 patients who underwent randomization, 309 were assigned to the sunitinib arm and 306 to the placebo arm. These patients were all "high risk of recurrence." Sunitinib recipients received 50 mg for a

year on a 4 of 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 to not reached) in the sunitinib group and 5.6 years (95% CI: 3.8–6.6) in the placebo group (HR: 0.76; 95% CI: 0.59–0.98; P = 0.03). The adverse effects observed in sunitinib recipients were consistent with its known toxicity profile. As such, the results from this trial support the potential for sunitinib as a treatment option in the adjuvant setting with a DFS advantage. However, overall survival endpoints have not yet been reported.

7.3.4. PROTECT trial



The PROTECT study, completed recently in 2017, was a phase 3 randomized clinical trial that evaluated the efficacy of adjuvant pazopanib as compared to placebo in preventing RCC recurrence in intermediate to high-risk patients [63]. The trial enrolled 1538 participants and the majority of the pazopanib recipients received a revised dosage of 600 mg, daily for a year, following a dose reduction from 800 mg which caused severe side effects. The interventions were evaluated by comparing DFS as the primary endpoint measure between the two trial arms. The study did not meet its primary endpoint and indicated no significant benefit of pazopanib-600 mg in prolonging DFS as compared to placebo (HR: 0.86; 95% CI, 0.70–1.06; P = 0.165). However, a subgroup analysis of pazopanib-800 mg recipients indicated a 31% decline in DFS (HR, 0.69; 95% CI, 0.51–0.94; *P* = 0.02). While the DFS results were conflicting between the 600 mg and 800 mg groups, the study reported similar adverse event profiles between both the groups.

7.3.5. Comparison of current adjuvant trial design

The differing outcomes that have been indicated in the current set of completed trials may be accounted for by the distinct sample groups, dose regimens, risk assessment criteria and trial methods [60–63]. This collectively represents a fundamental limitation that underscores all current adjuvant clinical trials. First, the patient inclusion criteria characteristically differ, in multiple ways, across all adjuvant trials [60–63]. For example, in the S-TRAC trial, the selected sample exclusively included patients with late-stage, loco-regional, clear-cell RCC while other trials such as the ASSURE, ARTISER and PROTECT trials used a less restricted criteria and included patients with stage 1 or stage 2 tumors and non-clear-cell histologies [60–63]. In addition, another major cause of heterogeneity lies in the risk assessment and stratification criteria as the scoring system used in the current set of adjuvant trials are not standardized, and hence this invariably contributes to a varied assessment of recurrence risk [60–63]. With respect to the conflicting sunitinib trials (S-TRAC vs. ASSURE), additional sources of variation

that might have led to inconsistent outcomes include varying dose regimens, specifically with respect to the midtrial dose reductions for sunitinib, as well as differing trial criteria for establishing disease status and assessing primary end point status [61, 62, 64].

7.4. Targeted immunomodulatory therapy

The development of therapy that targets oncogenic signaling pathways has advanced the treatment landscape for patients with advanced renal cell carcinoma. While nonspecific immunotherapy with IL-2 and IFN-α was the former mainstay in the management of metastatic disease, there was a shift away from it with the advent of targeted therapy which yielded relatively better response rates [32–34, 48–54, 65–68]. However, over the last couple of years, cancer immunotherapy has been revisited and, as a result, targeted immunomodulatory therapy, involving novel immunomodulating agents, has been reincorporated in combination therapy regimes for mRCC management—hence allowing for an induced immuonologic effect in addition to the inhibitory effect on tumor biology and microenvironment [69, 70]. This has been inspired in part by disease resistance that is progressively manifesting itself against standard targeted therapy in the landscape of metastatic disease management [69, 70].

Given that multiple mechanisms are employed by tumors to evade and suppress the immune system, research toward better understanding those mechanisms of immunomodulation has been critical in informing the therapeutic landscape [69, 71]. Particularly, an improved understanding of the factors regulating the antitumor immune response has led to the development a novel form of cancer immunotherapy involving checkpoint inhibitors and other immune therapies such as T-cell agonists, adoptive T-cell therapies and novel vaccines which are being evaluated across different trials for metastatic RCC [69, 71].

7.5. Immune checkpoint inhibitors

Immune checkpoints serve a critical protective function of preventing immune response against host cells through a series of complex interactions [71–73]. However, investigation into the pathogenic mechanisms of RCC revealed that cancer cells can induce similar interactions with host checkpoint receptors and can hence suppress the human immune response [71–73]. Immune checkpoint inhibitors counter these molecular mechanisms through which tumor cells evade immune recognition [71–73].

Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) are currently the most well understood inhibitory checkpoint receptors [71–73]. The PD-1/PD-L1 axis involves an inhibitory interaction between a T-cell inhibitory ligand PD-L1, expressed on tumor cell surface, and a PD-1 receptor on the lymphocyte [71–73]. Hence, mimicking this interaction ultimately allows tumor cells to evade the adaptive immune response through suppression of T-cell function. The CTLA-4 pathway is similarly exploited by tumor cells [71–73]. During an adaptive immune response, immune activation occurs through an interaction between the T-cell receptor (TCR) and the antigen-presenting cell (APC) along with the co-stimulation of CD28 on the T cell [71–73]. This activation is negatively regulated by an inhibitory interaction between CTLA-4 and its ligands—CD80 or CD86 [71–73]. Thus, the targeted inhibition of these checkpoint receptors through targeted antibodies, in both the pathways mentioned above, could allow for T-cell activation and effective immune function [71–73].

The first checkpoint inhibitor which demonstrated a survival benefit in patients with metastatic RCC was nivolumab—an anti-PD1 monoclonal antibody [74]. The inhibitor, which received FDA approval in 2015 based on the results from a trial evaluating nivolumab versus everolimus, is effective in yielding positive response rates when used for treatment of advanced RCC in patients who have undergone prior anti-angiogenic therapy [74]. Apart from nivolumab, multiple other checkpoint inhibitors are being currently evaluated in different trials against advanced RCC [71–73].

7.6. Immunomodulatory therapy in the adjuvant setting

Given their recent development, many immune checkpoint inhibitors are still being evaluated for their efficacy and toxicity against metastatic RCC, and hence investigation of these inhibitors in the adjuvant setting has been limited. Currently, there are a few ongoing clinical trials that are evaluating different checkpoint inhibitors in both the adjuvant setting as well as the neo-adjuvant (presurgery) setting (**Table 3**) [75–78].

The *IMmotion*, *KEYNOTE-564*, and *CheckMate 914* are phase III trials evaluating the efficacy and safety of adjuvant atezolizumab, pembrolizumab, and nivolumab/ipilimumab (combinational regimen) respectively in prolonging the DFS of RCC patients who are at high risk of disease recurrence post nephrectomy [75, 77, 78]. In addition to the adjuvant trials, an ongoing study in the neo-adjuvant setting includes the PROSPER trial which is evaluating the efficacy of pre-nephrectomy nivolumab [75]. These trials, which have either started already or are expected to begin later this year, are currently in their recruitment or pre-recruitment phases and are anticipated to be completed by 2022–2024. [75, 77, 78] Apart from these clinical

Adjuvant clinical trials in RCC using immune therapies

Authors	Intervention	Patient population	Design	No. of patients	Outcome
Pizzocarro et al. [32]	IFN-α2b vs. placebo	Robson stages II and III (T3aN0M0 and T3bN0M0 or T2/3N1-3M0)	Multicenter, randomized, controlled trial	247	5-year OS: 0.665 (control) vs. 0.660 (treatment) (HR 1.040; 95% CI, 0.671–1.613, P ¼ _0.861) 5-year DFS: 0.671 (control) vs. 0.567 (treatment) (HR 1.412; 95% CI, 0.927–2.149, P ¼ _0.107)
Passalacqua et al. [34]	IL-2 and IFN-α _v observation	pT1, T2, T3 a-b-c; pN0-pN3,M0M	Multicenter, randomized, controlled trial	310	5-year DFS: 0.73 (control) vs. 0.73 (treatment) 10-year DFS: 0.60 (control) vs. 0.73 (treatment) (HR 0.84; 95% CI, 0.54–1.33, P ¼ _0.47)

Adjuvant clinical trials in RCC using immune therapies					
Authors	**Intervention**	**Patient population**	**Design**	**No. of patients**	**Outcome**
Clark et al. [48]	IL-2 vs. observation	T3b-4 or N1-3 (LA) or M1	Multicenter, randomized, controlled trial	69 total; 44 LA, 25M1 disease	2-year DFS: 48% (control in LA patients) vs. 53% (treatment in LA patients) (P ¼ _0.73) 2-year OS: 77% (control in LA patients) vs. 86%
Messing et al. [33]	IFN-α-NL vs. observation	pT3–4a and/or node-positive	Multicenter, randomized, controlled trial	283	At 10.4 years median follow-up: Median survival: 7.4 years (control) vs. 5.1 years (treatment) (P ¼ _0.09). DFS: 3.0 years (control) vs. 2.2 years (treatment) (P ¼ _0.33)
Atzpodien et al. [35]	IL-2 and IFN-α2a and intravenous 5 vs. fluorouracil	pT3b/c pN0 or pT4pN0), pN, complete resection of tumor relapse or solitary metastasis (R0)	Multicenter, randomized, controlled trial	203	At median follow-up of 4.3 years: 2-year OS: 91% (control) vs. 81% (treatment) 5-year OS: 76% (control) vs. 58% (treatment) 8-year OS: 66% (control) vs. 58% (treatment) (P ¼ _0.0278) 2-year DFS: 62% (control) vs. 54% (treatment) 5-year DFS: 49% (control) vs. 42% (treatment) 8-year DFS: 49% (control) vs. 39% (treatment) (P ¼ _0.2398)
Aitchison et al. [36]	IL-2 and IFN-α2a and intravenous 5-fluorouracil	T3b-c,T4 or any pT and pN1 or pN2 or positive microscopic margins or microscopic vascular invasion	Multicenter, randomized, controlled trial	309	3-year DFS: 50% (control) vs. 60% (treatment) (HR 0.87; 95% CI, 0.63–1.20) 5-year OS: 60% (control) vs. 68% (treatment) (HR 0.91; 95% CI, 0.60–1.38)

Adjuvant clinical trials in RCC using immune therapies					
Authors	**Intervention**	**Patient population**	**Design**	**No. of patients**	**Outcome**
Galligioni et al. [39]	Autologous irradiated tumor cells and BCG vs. observation	Stages I, II, and III	Prospective, randomized, controlled trial	120	At 61 months median follow-up: 5-year OS: 78% (control) vs. 69% (treatment) 5-year DFS: 72% (control) vs. 63% (treatment)
Adler et al. [40]	Autologous irradiated tumor cells & BCG & hormone vs. hormone	All stages	Prospective, randomized, controlled trial	43	Trend for prolongation of DFS for stage I, II, and III (P o.1)
Wood et al. [41]	Autologous, tumor-derived heat-shock protein (glycoprotein 96)-peptide complex (HSPPC-96; vitespen) vs. observation	cT1b–T4 N0 M0, or cTanyN1-2M0Multicenter	Multicenter, randomized, controlled trial	819	At 1.9 years median follow-up: recurrence: 39.8% (control) vs. 37.7% (treatment) (HR 0.923; 95% CI, 0.729–1.169, P ¼ _0.506) OS not mature
Jocham et al. [42]	Autologous renal tumor cells (Reniale)	pT2–3b pN0–3	Multicenter, randomized, controlled trial	558	At 5-year follow-up: DFS: 67.8% (control) vs. 77.4% (treatment) (P ¼ _0.0204). At 70-month follow-up: DFS: 59.3% (control) vs. 72% (treatment). HR for tumor progression: 1.58 (95% CI 1.05–2.37) and 1.59 (1.07–2.36) (P ¼ _0.0204)

IFN, interferon; IL, interleukin; NL, neutral lymphoblastoid; LA, locally advanced; BCG, bacillus Calmette-Guérin; CI, confidence interval; LA, locally advanced; HR, hazard ratio; M, metastatic; OS, overall survival; DFS, disease-free survival.

Table 3. Adjuvant clinical trials in RCC using immune therapies.

studies, there are several checkpoint inhibitors that are in development as well as others that are currently being evaluated in trials for mRCC and would subsequently be assessed in the adjuvant setting [71–73] (**Tables 4–6**).

7.7. Change of practice

The European Association of Urology Renal Cell Cancer Guidelines Panel, which includes patient representatives and clinicians, considered a number of different scenarios to determine what would be required from S-TRAC to change practice. The decision on practice change

Trial name.	Trial ID	Intervention	Sample size	Inclusion criteria (histology; stage/ grade)	Primary endpoint measure	Completion date
ARISER	NCT00087022	Girentuximab	864	**ccRCC**; T1b,N0, NX,MO, T2,N0, NX,MO (grade ≥ 3) (risk: intermediate-High)	DFS,OS	2014
ASSURE	NCT00326898	Sorafenib or Sunitinib	1943	**Any**; pT1bN0M0 (grades 3–4), pT2-4N1-3M0 (risk: intermediate-high)	DFS	2016
S-TRAC	NCT00375674	Sunitinib	615	**ccRCC**; pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 (risk: High)	DFS	2016
PROTECT	NCT01235962	Pazopanib	1500	**ccRCC**; pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 (risk: intermediate-high)	DFS	2017

Table 4. RCC adjuvant clinical trials that have been completed.

was taken in the context of the data from ASSURE. Results showed that only 1 out of 15 (6%) of the panel would change their standard of care when considering the DFS and OS closest to S-TRAC (DFS: HR 0.75, $p < 0.05$; OS: HR 1.0, $p > 0.05$). Standard practice would only be significantly influenced by a significant survival benefit. In addition, kidney cancer patients from the International Kidney Cancer Coalition (IKCC) participated in a questionnaire about

Trial name.	Trial ID	Intervention	Sample size	Inclusion criteria (histology; stage/ grade)	Primary endpoint measure	Estimated completion date
SORCE	NCT00492258	Sorafenib	1420	**Any**; pT1a N0M0 (grade 4), pT1b N0M0 (grades 3–4), pT2-4N0M0, pT1b-4N1M (risk: intermediate-high)	DFS	2019
ATLAS	NCT01599754	Axitinib	592	**ccRCC**; pT2-4N0M0 or pTxN1M0 (risk: high)	DFS	2019
EVEREST	NCT01120249	Everolimus	1218	**Any**; pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 (risk: intermediate-high)	DFS	2021

Table 5. Current set of adjuvant clinical trials that are still in progress.

Trial name	Trial ID	Intervention	Estimated enrollment	Primary endpoint measure	Start date	Completion date
PROSPER	NCT03055013	Nivolumab (pre-Nx)	766	DFS	February 2, 2017	2022
KEYNOTE-564	NCT03142334	Pembrolizumab	950	DFS	June 9, 2017	2022
CheckMate 914	NCT03138512	Nivolumab, ipilimumab	800	DFS	July 3, 2017	2023
IMmotion010	NCT03024996	Atezolizumab	664	DFS	January 3, 2017	2024

Table 6. Ongoing adjuvant and neo-adjuvant clinical trials.

the implications for STRAC. The results lacked clarity. Twenty-two patient representatives from the IKCC network were asked what degree of PFS advantage would be needed to justify taking sunitinib for 1 year. Approximately one-third of patients favored not taking sunitinib when faced with the S-TRAC results [79].

Recently, on November 2017, the FDA approved the use sunitinib for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy. The approval was based on (S-TRAC) trail.

8. Conclusions and future directions

Targeted therapy has become the current mainstay in the management of metastatic RCC and its success with advanced stage disease has been the driving force behind the increasing number of targeted therapy trials in the adjuvant setting. The emergence of immune checkpoint inhibitors in the last couple of years has further led to important advances in our understanding and management of mRCC. However, many ongoing trials are yet to be completed in both cases and there is ample potential for further investigation—especially with respect to combinational therapy regimes. This includes the combination of TKIs with immune therapies (e.g., NCT01513187: Pazopanib with Interferon Alfa 2-A), combination of TKIs with chemotherapeutics (e.g., NCT00556049: Sunitinib with Gemcitabine), and the combination of anti-VEGF antibodies and mTOR inhibitors (e.g., NCT01399918: bevacizumab and everolimus). All of these treatments may be of interest for future adjuvant trials in RCC if they are found to be effective in stage IV disease. However, they may have more side effects, making them less suitable in particular for adjuvant treatment. Nonetheless, the current information, which has resulted from all the progress in the field, remains incongruent. While the current set of completed adjuvant clinical trials have provided negative or conflicting results (ARISER, PROTECT, S-TRAC vs. ASSURE), there are additional large-scale trials that are still in progress. The existing trial design has several limitations, the key one being the overall lack of standardization seen across various assessment criteria. Future directions include

incorporating a genetic recurrence score to evaluate risk of relapse in patients, developing an adequate and an objectively standardized adjuvant trial design, identifying novel biomarkers and evaluating novel drug targets.

That based on results from current trials, the "high risk for recurrence" RCC patient population (T3-T4, grade 3-4) may benefit from adjuvant sunitinib providing DFS advantage but pending OS results. Patients, in this category, interested in adjuvant therapy would benefit from a discussion with an oncologist regarding the potential benefits and risks of adjuvant treatment post kidney cancer surgery. Overall, the landscape of adjuvant treatment in nonmetastatic high-risk RCC is expected to expand and to further develop in the coming years.

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