Adjuvant therapy in renal cell carcinoma: does higher risk for recurrence improve the chance for success?

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The success of targeted therapies, including inhibitors of the vascular endothelial growth factor pathway or the mammalian target of rapamycin, in the treatment of metastatic renal cell carcinoma led to interest in testing their efficacy in the adjuvant setting. Results from the first trials are now available, with other studies due to report imminently. This review provides an overview of adjuvant targeted therapy in renal cell carcinoma, including interpretation of currently available conflicting data and future direction of research. We discuss the key differences between the completed targeted therapy adjuvant trials, and highlight the importance of accurately identifying patients who are likely to benefit from adjuvant treatment. We also consider reasons why blinded independent radiology review and treatment dose may prove critical for adjuvant treatment success. The implications of using disease-free survival as a surrogate end point for overall survival from the patient perspective and measurement of health benefit have recently been brought into focus and are discussed. Finally, we discuss how the ongoing adjuvant trials with targeted therapies and checkpoint inhibitors may improve our understanding and ability to prevent tumor recurrence after nephrectomy in the future.

Key words: adjuvant therapy, renal cell carcinoma, S-TRAC, ASSURE, PROTECT

Introduction

Over 300,000 cases of kidney cancer are diagnosed worldwide each year and renal cell carcinoma (RCC) accounts for 90% of these cancers [1, 2]. The proportion of RCC cases is increasing each year, and this trend is projected to continue until 2035 [3]. The common use of medical imaging has dramatically increased the incidental detection of RCC, and today approximately 65% and 16% of patients with localized and loco-regional disease, respectively, are diagnosed in this way [4]. Surgical resection (partial or radical nephrectomy) followed by observation is the standard of care for RCC tumors [2, 5]; however, depending on tumor stage and other risk factors at diagnosis, up to 40% of patients with RCC will develop metastatic disease [6, 7]. In a subset of these patients, comprising approximately 15% of all patients with nonmetastatic RCC, who are categorized as high risk for recurrence on the basis of the University of California Los Angeles Integrated Staging System (UISS) criteria [i.e. T3, no or undetermined nodal involvement, Fuhrman grade ≥ 2, Eastern Cooperative Oncology Group performance status (ECOG PS) prenephrectomy ≥ 1, and T4 and/or nodal involvement], the risk is even greater, with approximately 60% rate of recurrence over a 5-year period [8]. As such, effective adjuvant therapy for RCC is an unmet medical need for patients with features that confer a high risk of recurrence. Although, the prognosis for patients with metastatic RCC has improved in the past decade with the availability of a number of molecularly targeted agents, none of these therapies is curative.

Several clinical trials, often after successful studies in the metastatic setting, have evaluated different strategies for adjuvant treatment in RCC, including cytokine therapy, radiotherapy, hormone therapy, and vaccine-based therapy [9–19]. These study results have all proven to be negative. A recent trial evaluated the efficacy of a chimeric monoclonal antibody targeting the carbonic anhydrase IX (CAIX) protein that is overexpressed in clear cell RCC [20]. Results showed no significant difference in disease-free survival (DFS) or overall survival (OS) [21]. Subgroup analysis reported improved DFS and OS (P = 0.01 for both) in a small proportion (33%) of patients with high...
Targeted therapy in metastatic RCC

The increased activity of the hypoxia-induced factors (HIF), which can be induced by loss of the von Hippel Lindau gene activity or via abnormal activation of the mTOR pathway, leads to overexpression of hypoxia-regulated proteins, including VEGF, and is implicated in the pathology of clear cell RCC [20]. Multiple agents have been developed to specifically target the VEGF (i.e. sorafenib, sunitinib, pazopanib, axitinib, and bevacizumab) [23–29] or mTOR (i.e. temsirolimus and everolimus) [30, 31] pathways. These agents significantly improve OS in patients with metastatic RCC [32–34]. To date, no reproducible and validated specific biomarker with a predictive value for efficacy of any of these available agents has been identified [35]. Consequently, the success of targeted therapies in the metastatic setting inspired testing them in the adjuvant setting in patients at high risk for tumor recurrence after nephrectomy.

Identifying patients at high risk for tumor recurrence

A number of risk stratification nomograms have been developed to assess the risk for relapse in patients with nonmetastatic RCC. All are based on the American Joint Committee on Cancer 2002 or 2010 tumor, lymph nodes, and metastasis (TNM) staging system, but include additional clinical variables. The tumor stage, size, grade, and necrosis (SSIGN) score by the Mayo Clinic was designed to predict cancer-specific survival of patients with clear cell RCC [36]. The Leibovich score (Mayo Clinic PFS score) takes into account the tumor stage, regional lymph node status, tumor size, nuclear grade, and histologic tumor necrosis and is specifically designed to predict progression to metastatic RCC after nephrectomy for patients with clinically localized clear cell RCC [37]. The UISS criteria take into account the TNM stage, Fuhrman grade, and ECOG PS, and are designed to stratify patients into risk groups and predict survival [38, 39]. A study by Ficarra et al. showed that the SSIGN score offered a better stratification of clear cell RCC compared with the UISS model, with area under the receiver operating characteristics curves of 0.870 versus 0.832, respectively [40]. Each one of the adjuvant targeted-therapy trials described below used one of these tools to stratify patients into risk groups (Table 1). Other risk stratification tools based on molecular features include the ClearCode34, a 34-gene classifier model to assess risk for recurrence [41], and the 16-gene Recurrence Score [42], a new prognostic gene expression signature assay to identify patients with high risk of recurrence.

Completed trials with inhibitors of the VEGF pathway

To date, three of the adjuvant trials in the targeted therapy era have been reported: ASSURE, S-TRAC, and PROTECT.

The ASSURE trial randomized (1:1:1) 1943 patients with localized or loco-regional RCC at moderate or high risk (≥T1b G3–4 and/or N+; Table 1) for relapse after nephrectomy to receive sunitinib (50 mg/day), sorafenib (400 mg twice daily), or placebo for 1 year. The high rate of toxicity-related treatment discontinuation in this trial led to a mid-study amendment that allowed patients to initiate treatment at a reduced dose of both sorafenib and sunitinib. At the interim analysis, the Data Safety Monitoring Committee recommended release of the results. The results showed no difference in DFS or OS in patients treated with sunitinib or sorafenib versus placebo [43]. Subgroup analysis of patients (n = 1069) with high-risk (pT3–T4 or N+) clear cell RCC also reported no difference in DFS or OS among treatment groups [44]. The most commonly (>10% of patients) occurring grade 3/4 adverse events in sunitinib- and sorafenib-treated patients, respectively, were hypertension (17% and 16%), fatigue (18% and 7%), hand–foot syndrome (15% and 33%), and rash/desquamation (2% and 15%) [43].

In the S-TRAC trial, 615 patients with loco-regional clear cell RCC at high risk (≥T3 and/or N+; Table 1) for relapse after nephrectomy were randomized (1:1) to receive 50 mg/day sunitinib or placebo for 1 year. S-TRAC met its primary end point and demonstrated that patients treated with sunitinib had a statistically significant and clinically meaningful 24% reduction in risk of DFS event occurrence or death compared with those treated with placebo [hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.59–0.98; P = 0.03; median 6.8 versus 5.6 years, respectively] based on blinded independent central review [45]. There was no difference in OS, although it is important to note that the data were not mature at the time of publication. Grade 3/4 adverse event occurring in >5% of sunitinib-treated patients included hand–foot syndrome (16%), neutropenia (8.5%), and hypertension (7.8%).

The PROTECT trial randomized (1:1) 1538 patients with loco-regional at moderate or high risk (≥T1b G3–4 and/or N+; Table 1) for relapse after nephrectomy to receive 800 mg/day pazopanib or placebo for 1 year. Similar to the ASSURE trial, the starting dose was reduced from 800 to 600 mg to improve tolerability, but the primary end point was modified to DFS in the intent-to-treat (ITT) 600-mg group. Results showed no significant differences in DFS between the pazopanib 600-mg ITT group versus placebo (HR 0.862; 95% CI 0.699–1.063; P = 0.165). However, DFS in pazopanib 800-mg ITT patients (N = 403), a secondary end point, achieved a 31% reduction in relapse risk with pazopanib versus placebo (HR 0.693; 95% CI 0.510–0.943) [46]. A 20% reduction in relapse risk was observed.

expression CAIX (score ≥200 versus ≤100) [22]. Despite the considerable effort to develop effective adjuvant therapies for RCC, no therapy has been implemented in clinical practice to date.

The success of targeted therapies, including inhibitors of the vascular endothelial growth factor (VEGF) pathway or the mammalian target of rapamycin (mTOR), in the treatment of metastatic RCC led to interest in testing their efficacy in the adjuvant setting. A few of these trials have been completed or are nearing completion, and others are ongoing. This review provides an overview of adjuvant targeted therapy in RCC, including where we are now and where we are going. We highlight the importance of identifying patients who are likely to benefit from adjuvant treatment and consider reasons why dose may prove critical for treatment success. The implications of using DFS as a surrogate end point for OS are also discussed.
in the entire population with pazopanib versus placebo (HR 0.802; 95% CI 0.675–0.954) [46]. The most commonly (>10% of patients) occurring grade 3/4 adverse events in pazopanib-treated patients included hypertension (25%) and increased alanine aminotransferase (16%). The safety profile was similar between patients treated with 600 and 800 mg pazopanib.

Examining differences among completed trials

Of the three completed targeted-therapy trials, S-TRAC is the only study to meet its primary end point: a reported significant difference in DFS in sunitinib- versus placebo-treated patients. The lack of benefit in PROTECT could be due to a lack of efficacy with 600 mg pazopanib. However, the different outcomes achieved with adjuvant sunitinib in ASSURE versus S-TRAC necessitate a closer examination of the design of each of these trials. Differences in baseline risk categories, dosing, and length of treatment may have impacted the outcome in these trials.

Blinded independent central review.

Blinded independent central review may reduce potential bias, especially when an active agent with known safety profile is tested against placebo. The lack of a blinded independent central review may have contributed to the difference in DFS outcomes among the adjuvant trials: ASSURE had no blinded independent central review and PROTECT had blinded central review at baseline only but not at relapse. Conversely, in S-TRAC, blinded independent central review of imaging scans was conducted both at baseline (to ensure exclusion of patients with macroscopic residual disease or metastatic disease) and at recurrence. When recurrence was assessed by the S-TRAC investigator, there was a similar improvement in median DFS in patients treated with sunitinib (6.5 years) versus placebo (4.5 years), but the difference was not statistically significant (HR 0.81; 95% CI 0.64–1.02; P = 0.08) [45]. Despite the high concordance found between the investigator and blinded independent central review in the assessment of DFS, investigators called relapse earlier than the blinded independent central review [45]. Altogether, these findings further support the importance of a blinded central review of imaging scans in adjuvant treatment trials.

Risk categories and patients likely to benefit from adjuvant therapy.

Another central difference among the completed (or terminated) trials in targeted therapy is the baseline risk of the patient populations. S-TRAC enrolled mainly patients at higher risk (T3 and/or N+) for RCC recurrence compared with ASSURE and PROTECT, which included patients with low, intermediate, or high risk (Table 1). Approximately one-third of the patients in ASSURE had T1 or T2 tumors and would have been excluded from S-TRAC enrollment. The risk overlap between patient populations in ASSURE, S-TRAC, and PROTECT is illustrated in Figure 1. Similarly, a study in colon cancer demonstrated a clear clinical benefit with adjuvant therapy in patients with resected stage III (node-positive) disease, while the benefit in patients with resected stage II (node-negative) disease remains debatable [47].
With the positive outcome of S-TRAC, it is conceivable that patients with clear cell RCC at higher risk for tumor recurrence are more likely to benefit from adjuvant targeted therapy. Indeed, a prespecified subgroup analysis of patients at higher risk \([T3 \text{ high (N0 or Nx, Fuhrman grade } \geq 2, \text{ ECOG PS } \geq 1) + T4 + \text{ any T/N}+]\) than the overall population of S-TRAC showed a greater increase in median DFS with sunitinib versus placebo (HR 0.74; 95% CI 0.55–0.99; \(P = 0.04\); median 6.2 versus 4.0 years, respectively) [45]. In contrast, subgroup analysis of ASSURE patients with clear cell RCC at higher risk \((\geq T3 \text{ or N+})\) for recurrence revealed no such increase in DFS or OS with sunitinib or sorafenib versus placebo [44]. However, measured or unmeasured differences in subgroup populations, such as the imbalance in the T3-low (N0 or Nx, any Fuhrman grade, ECOG PS 0, or Fuhrman grade 1, ECOG PS 1) versus high-risk groups limit the extrapolation of these results to the high-risk patient population enrolled in S-TRAC. Furthermore, this could be attributed to other differences between the two trials (e.g. dosing), which are discussed below.

**Dose matters.** The starting dose and the maintenance of that dose over the course of the study may have impacted DFS outcomes in the completed targeted-therapy trials. On point, in both ASSURE and PROTECT, the starting dose was modified mid-study due to toxicity (Table 1).

In ASSURE, 69.6% of the patients received the sunitinib 50 mg/day starting dose compared with 100% of patients who received the sunitinib starting dose (50 mg/day) in S-TRAC [43, 45]. The remaining patients in ASSURE started sunitinib treatment at a reduced dose of 37.5 mg. Moreover, patients in ASSURE were allowed dose reductions to 25 mg, whereas patients in S-TRAC were limited to 37.5 mg. The difference in dosing patterns resulted in a lower median cumulative dose of sunitinib for patients in ASSURE compared with S-TRAC (6800 mg versus 9638 mg, respectively; Table 1).

A clear relationship between dose exposure and efficacy was demonstrated in the PROTECT trial, in which patients treated with the initial starting dose of pazopanib (800 mg/day) had a greater risk reduction in DFS compared with patients treated with a lower dose (600 mg/day), 31% versus 14%, respectively [46]. A relationship between dose exposure and improved clinical outcome has been also demonstrated by Houk et al. in patients with metastatic RCC, in which increased exposure to sunitinib resulted in longer time to tumor progression and OS [48]. Furthermore, maintaining the dose level throughout the study is important given the angio preventative effect of antiangiogenic therapies, i.e. their ability to prevent neovascularization of microscopic tumors [49].

**Patient perspective and measurement of health benefit**

Although improving OS in patients is the ultimate goal of adjuvant therapy, OS is impacted not just by the study drug but also by post-study treatments and other factors that might contribute to patient survival or death. Other practical limitations for using OS as an end point include the need for a large sample size and extended follow-up period, particularly for slow-progressing cancers. As a result, DFS or recurrence-free survival have commonly been the primary basis for approval of adjuvant treatments in various tumor types, including colon cancer, breast cancer, melanoma, and gastrointestinal stromal tumors [50–55]. Nevertheless, delaying recurrence with adjuvant therapy offers multiple benefits for the patient, including feeling free of disease while increasing the chance of a better therapy to be available at relapse, and may also serve to reduce health care resource utilization costs [56].

The European Association of Urology (EAU) Renal Cell Carcinoma Guidelines panel recently updated their recommendation

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**Figure 1.** Risk overlap between patient population in ASSURE, S-TRAC, and PROTECT. AJCC, American Join Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; N, node; M, metastasis; T, tumor; TNM, tumor, lymph node, metastasis; UISS, University of California of Los Angeles Staging System.
on adjuvant therapy, in which they provided a weak recommendation not to use adjuvant sunitinib following surgically resected high-risk clear cell RCC [57]. The panel’s decision was based on a meta-analysis of data from the ASSURE and S-TRAC trials, the toxicity level in each trial, and a survey of 22 patient representatives, i.e. patients with nonmetastatic disease who had previously undergone surgery, and who participate in the International Kidney Cancer Coalition (IKCC) [57]. Not surprisingly, the meta-analysis that was based on aggregate trial-level (rather than patient-level) data found a nonsignificant difference in DFS, probably due to larger enrollment in ASSURE, and the other inherent differences that were not taken into account between the two trials discussed earlier. Given the differences between the two trials, the results from the trial-level meta-analysis should be interpreted with caution. Specifically, the efficacy results of the ITT population in ASSURE are not indicative of the efficacy in the high-risk RCC population enrolled in S-TRAC. Therefore, the results of the trial-level meta-analyses are also not indicative of the efficacy in the high-risk RCC population. Analysis of patient-level data from comparator arms across the two trials would have been more appropriate to investigate the impact of patient characteristics of treatment outcome [58].

When the patient representatives from IKCC (n = 22) were further asked ‘After surgery for kidney cancer, if your doctor told that you are at high risk of recurrence (spread), would you consider taking sunitinib (Sutent) for 1 year in the hope you could delay the onset of recurrence even if your overall survival was not improved?’ They were also asked, ‘What degree of DFS advantage would be needed to justify taking sunitinib for 1 year knowing that there is no improvement in OS?’ When presented with a range of DFS-suggested responses (any DFS, DFS ≥6 months, DFS ≥1 year, DFS ≥2 years, or DFS ≥5 years), more than two-thirds of respondents answered, ‘yes, it is justified to take sunitinib’ [57]. It is possible that patients in the adjuvant setting without demonstrated metastasis may be less willing to continue therapy when they encounter toxicity; therefore, the perspective offered here may not translate to a reality of many patients sticking with therapy in a true clinical setting.

When the 15 panel members were asked to vote anonymously if they agree with the following statement: ‘Adjuvant sunitinib following surgically resected high-risk clear-cell RCC is not recommended. Grade of recommendation: weak’, about 80% of them were in agreement. However, the strength of the EAU recommendation against using adjuvant sunitinib was ultimately rated as weak because it was based on only two clinical studies with conflicting results, and the preference of the patient representatives to have this treatment option despite the toxicity and lack of OS data [57].

Patient preference to delay recurrence, even when the improvement in OS is modest or unclear, is also evident in studies of other tumor types. When women with early-stage breast cancer were asked to rate the survival benefit that would justify 6 months of adjuvant chemotherapy, most of them considered the treatment worthwhile for relatively modest DFS improvements [59, 60]. Similarly, patients with low-risk melanoma were willing to accept the toxicity of interferon-α in exchange for a 4%–10% improvement in recurrence-free survival [61]. Although OS remains the goal of adjuvant therapy, improvement in DFS or recurrence-free survival is highly valued by patients.

### Ongoing trials

#### Trials assessing utility of targeted therapy

Three ongoing clinical trials, SORCE, ATLAS, and EVEREST, are assessing the utility of targeted therapy in the adjuvant setting.

In the SORCE trial (NCT00492258), patients with clear or nonclear cell histology at intermediate or high risk for RCC recurrence after nephrectomy were treated with sorafenib 400 mg twice daily versus placebo for 1 or 3 years. Similar to ASSURE, the initial starting dose was reduced, in this case from twice- to once-daily 400 mg, to address toxicity issues [62]. Although the study completed recruitment in 2012, the final results are not yet published, except for one report of fatal sorafenib-associated idiosyncratic hepatotoxicity [63]. The results of the 3-year treatment arm in this study will be intriguing as to the impact of chronicity of treatment.

In the ATLAS trial (NCT01599754), patients with clear cell RCC at intermediate or high risk for tumor recurrence after nephrectomy are treated with axitinib 5 mg twice daily or placebo for up to 3 years. This study is ongoing, but fully enrolled and no longer recruiting participants. The projected completion date for collecting data for the primary outcome measure is September 2018.

In the EVEREST trial (NCT01120249), patients with clear or nonclear cell histology at intermediate or high risk for RCC recurrence after nephrectomy are being treated with everolimus 10 mg daily or placebo. The primary completion date is expected in October 2021.

#### Adjuvant therapy with checkpoint inhibitors

Agents that block the interaction between the immune-checkpoint receptor programmed death-1 (PD-1) and its ligands have demonstrated efficacy in metastatic RCC. In pretreated mRCC patients, nivolumab, a PD-1 inhibitor, was associated with 5.4 months longer median OS and fewer grade 3/4 adverse events compared with everolimus [64]. Based on the success of checkpoint inhibitors in the metastatic setting, three ongoing trials examine the efficacy of these agents in the adjuvant and neo-adjuvant RCC settings.

The IMmotion010 trial (NCT03024996) examines the efficacy of atezolizumab versus placebo in patients with RCC with clear cell or sarcomatoid histologies at moderate or high risk (T2N0G4, T3aN0G3-4, T3b/cN0anyG, or TanyN+ anyG or had complete resection of limited metachronous/synchronous metastasis) of disease recurrence following nephrectomy [65]. This study is currently recruiting participants, and the primary completion date is expected in June 2022.

The PROSPER trial (NCT03055013) is comparing perioperative (neoadjuvant and adjuvant) nivolumab versus observation in patients with moderate- or high-risk (T2-4NxM0 or TanyN+) RCC undergoing nephrectomy. This study is currently recruiting participants, and the primary completion date is expected in July 2022.

The KEYNOTE-564 trial (NCT03142334) is currently recruiting participants and will be evaluating the efficacy of pembrolizumab versus placebo in patients with clear cell intermediate–high risk (T2N0G4 or sarcomatoid; T3N0anyG), high risk (T4N0anyG, TanyN+ anyG), or M1 with no evidence of RCC disease (presentation of not only the primary kidney tumor but also solid, isolated, soft-tissue metastases that can be completely resected at the
time of nephrectomy). The primary completion date is expected in November 2022.

The CheckMate 914 trial (NCT03138512) is currently recruiting participants, and will be comparing the combination of nivolumab plus ipilimumab versus placebo in patients with localized RCC who are at high risk (T2a N0G3-G4, T2b N0anyG, T3 N0anyG, T4N0anyG, TanyN + anyG) of relapse postnephrectomy. The primary completion date is expected in September 2022.

Future direction

The heterogeneous outcomes gleaned from the completed targeted-therapy trials call for better-designed adjuvant trials that include patients at high risk for recurrence, evaluate the tolerable dose for treatment and methods to maintain patients on it before the launch of a large randomized trial, and use blinded independent central review. The positive outcomes in S-TRAC suggest that patients with the highest risk for tumor recurrence after nephrectomy are more likely to benefit from adjuvant targeted therapy. The outcomes from the ongoing targeted-therapy trials (SORCE, ATLAS, and EVEREST), which included patients at intermediate or high risk for recurrence, will provide further clarification.

If indeed, only patients at the highest risk for RCC recurrence benefit from adjuvant therapy, how do we best define high risk? Given the variety of risk stratification tools used in the different adjuvant trials (TNM, Mayo Clinic PFS score, UISS, and UISS modified), it is very important to clearly define this population. According to S-TRAC, high risk is defined as RCC patients with T ≥ 3, N0 or Nx, M0, any Fuhrman grade and any ECOG PS, or any T, N+, M0, any Fuhrman grade, and any ECOG PS. The 16-gene Recurrence Score developed by Rini and colleagues to identify patients with high risk of recurrence [42] was recently validated in the RCC patient population in S-TRAC. The results confirmed the prognostic value of this assay, as the Recurrence Score was found to be associated with DFS, time to recurrence, and renal cancer-specific survival [66]. Interestingly, approximately 20% of the ‘high-risk’ patients in S-TRAC were classified as low risk based on the 16-gene assay. This further illustrates the importance that future studies must identify the criteria—based on genetic testing and/or clinical features—used to classify patients as being at high risk for recurrence. Ultimately, the goal is to develop tools that can specify which patients will benefit from a specific treatment option.

Another point for consideration is the potential benefit of prolonged adjuvant therapy in patients with RCC. Adjuvant therapy trials in patients with gastrointestinal stromal tumor have shown an advantage of long-term (3 years) versus short-term (1 year) treatment [55, 67]. Results from the ongoing ATLAS and SORCE trials may help clarify if there is an advantage to longer treatment periods (i.e. 3 years) with the adjuvant targeted therapies axitinib and sorafenib, respectively.

Discussion

Conclusions

To date, adjuvant therapy has not been available to patients with RCC who are at high risk for recurrence after nephrectomy as the majority of available data have not shown benefit. However, results from the S-TRAC trial show improvement in DFS for high-risk patients with sunitinib in the adjuvant setting. Toxicity in sunitinib-treated patients in S-TRAC was comparable to that in the metastatic setting (other than a greater incidence of hand-foot syndrome that was also seen in ASSURE), and was clinically manageable. Future efforts to improve outcomes in the adjuvant setting may focus on selection of patients at higher risk for recurrence based on clinical and/or molecular features. The outcomes of ongoing adjuvant trials may improve our understanding and ability to prevent tumor recurrence after nephrectomy in the future. However, until more data become available, enrollment into adjuvant trials should be encouraged, along with a discussion of the benefits and side-effects associated with adjuvant treatment.

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8. The CheckMate 914 trial (NCT03138512) is currently recruiting participants, and will be comparing the combination of nivolumab plus ipilimumab versus placebo in patients with localized RCC who are at high risk (T2a N0G3-G4, T2b N0anyG, T3 N0anyG, T4N0anyG, TanyN + anyG) of relapse postnephrectomy. The primary completion date is expected in September 2022.


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