Adjuvant Therapy for Localized High-Risk Renal Cell Carcinoma

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KEYWORDS

• Carcinoma • Renal cell • Chemotherapy • Adjuvant • Recurrence • Molecular targeted therapy • Immunotherapy

KEY POINTS

- Recurrence risk following nephrectomy for kidney cancer varies widely based on disease biology, and surveillance algorithms are designed to intensify surveillance for the highest-risk individuals.
- Targeted therapy with anti–vascular endothelial growth factor receptor agents advanced the management of metastatic disease but has proved to be disappointing in the adjuvant setting, with no agents showing an improvement in overall survival.
- Several immunotherapy-based adjuvant therapy protocols are ongoing and hold promise for a future adjuvant therapy.

INTRODUCTION

Early detection has led to stage migration toward smaller and more localized forms of kidney cancer, and many individuals experience outstanding outcomes. However, approximately 10% of individuals present with stage 3 disease[1] and up to 40% of small tumors have adverse pathologic characteristics found at surgery.[2] For these high-risk patients, despite removal of all visible disease, approximately 50% recur within 6 years.[3–7]

As in many solid tumors, there is interest in providing high-risk patients with an effective adjuvant therapy that could decrease the likelihood of disease recurrence and ultimately translate into improved overall survival (OS). Numerous adjuvant therapy trials for high-risk renal cell carcinoma (RCC) have been undertaken to evaluate a wide range of agents. However, only a single trial thus far, the S-TRAC trial has shown a disease-free survival (DFS) benefit.[4] Given the potential toxicities of sunitinib, the lack of an OS benefit, and the discordance of S-TRAC's findings with other adjuvant trials, most clinicians have not changed their current practice patterns and the National Comprehensive Cancer Network (NCCN) guidelines still endorse clinical trial as the preferred option.[8] This article reviews the concepts and clinical data pertaining to adjuvant therapy for localized, high-risk RCC.

PATTERNS OF RECURRENCE, RISK FACTORS, AND RISK STRATIFICATION

Between 20% and 40% of all patients with localized kidney cancer experience a recurrence following surgery, with nearly 50% of the highest-risk patients recurring within 6 years.[3,4,7] Most recurrences occur

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within the first 3 years of complete surgical resection; however, many occur even after 10 years following surgery.[9,10] The most common systemic sites of recurrence are the lung (64%), liver (11%), bone (15%), regional lymph nodes (9%), and the renal fossa (9%).[11] Rates of local recurrence are 1% to 6% following partial nephrectomy and 1% to 3% following radical nephrectomy, with or without systemic recurrences.[9,12]

Risk factors for recurrence include nuclear tumor grade (including Fuhrman), tumor stage, nodal involvement, microvascular invasion, necrosis, margin status, and high-risk features such as sarcomatoid or rhabdoid differentiation.[13] Specific histologic subtypes such as collecting duct, medullary, and clear cell kidney cancer may have the highest risk of dissemination.[13,14] Various series have attempted to show that histology is an independent predictor of outcome; however, all forms of renal cancer can behave aggressively.[14–16]

Risk stratification is critical for identifying a population at highest risk for recurrence, and several staging systems exist for the prediction of DFS. Most rely heavily on surgical pathologic data, such as pathologic T stage, tumor size, nuclear (Fuhrman) grade, and presence of necrosis, although a presurgical nomogram exists as well (**Table 1**).[17–21] Because these nomograms use slightly different criteria, the calculated risk of recurrence varies between them. In general, the more complex a model is, the more difficult it is to use because several histologic features may not be uniformly reported on from the surgical specimens.[22] Even among adjuvant trial patients with the highest risk, many of these nomograms still perform poorly.

Attempts have been made to move beyond traditional clinical and pathologic criteria and incorporate somatic genetic information to create more accurate prognostic models in the high-risk patient population. This information has included protein expression[23] and gene expression scores. A molecular classification system, although promising, would increase the cost and complexity of identifying patients at highest risk. Before widespread adoption, it will be important to understand whether they add incremental value justifying their use.

CONCEPTS UNDERLYING ADJUVANT THERAPY

The goal of adjuvant drug therapy is to provide additional therapy following treatment of the primary tumor in order to reduce the risk of disease recurrence and death by eliminating residual micrometastatic disease that is destined to recur. Adjuvant treatment differs from salvage therapy in that treatment is administered based on a perceived risk of disease recurrence, but before any definitive evidence of disease recurrence. Adjuvant therapy has been shown to be a successful therapeutic strategy in various solid tumor types, including cancers of the breast, testis, ureter, ovary, and melanoma. For cancers with a serum biomarker (eg, prostate-specific antigen), detection at this level may be a useful surrogate for residual disease burden; however, such a marker does not exist in RCC. As such, clinicians must rely on prognostic models to help identify patients in whom micrometastatic disease is likely to be present.

Successful development of a therapeutic adjuvant agent must overcome the following challenges:

1. Candidate adjuvant agents must be identified. Inferring that agents successful in metastatic disease will be effective in the adjuvant setting likely depends on the mechanism of action. For example, vascular endothelial growth factor (VEGF)–targeting agents, which inhibit angiogenesis, may not function well as inhibitors of micrometastatic disease, whose biology may be less reliant on angiogenesis and nonlethal pathway inhibition.[24,25]
2. Inclusion criteria must allow for robust trial enrollment in a reasonable time frame while ensuring patients have enough risk to benefit from adjuvant therapy.
3. There must be enough power to detect a small but modest benefit. Inclusion of lower-risk patients with fewer events may limit the power to detect a smaller, but meaningful, benefit.
4. Side effect profile of any adjuvant agent must be sufficiently acceptable to justify treatment in asymptomatic patients.
5. Relevant end points must be determined. DFS has been shown to be a useful surrogate of OS in some diseases, and is an US Food and Drug Administration (FDA)–sanctioned end point in colorectal cancer and melanoma.[26,27] Although used as the primary end point in adjuvant RCC trials, some investigators have called into question whether DFS is an appropriate surrogate for OS.[28,29] There are various advantages and disadvantages to these end points in the adjuvant setting (**Table 2**).
6. The median DFS in recent adjuvant clinical trials is more than 6 years, making trials long and expensive.[3–5] With OS in the setting of metastatic disease now greater than 3 years, showing an OS difference may require a study to be open for longer than 5 years.

Table 1
Kidney cancer prognostic systems

System	Study	T Stage	N Stage	M Stage	Tumor Size	Grade	Necrosis	Histology	ECOG	MVI	Clinical Symptoms	Gender
UISS	Zisman et al,[17] 2002	1997 T stage	X	X	—	—	—	—	X	—	—	—
SSIGN	Frank et al,[18] 2002	2002 T stage	X	X	(< or ≥5 cm)	X	X	—	—	—	—	—
Leibovich	Leibovich et al,[19] 2003	2002 T-stage	X	—	(0 or ≥10 cm)	X	X	—	—	—	—	—
MSKCC	Kattan et al,[20] 2001	1997 T stage	—	—	Continuous	X	X	Clear cell, papillary, chromophobe	—	X	X	—
Raj[a]	Raj et al,[21] 2008	—	X	—	Continuous	—	X	—	—	—	X	X

Abbreviations: ECOG, Eastern Cooperative Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center; MVI, microvascular invasion; SSIGN, stage, size, grade, and necrosis; UISS, University of California, Los Angeles, integrated staging system.

[a] Used prenephrectomy, thus N status, tumor size, and necrosis based on imaging; all others used postnephrectomy and use pathologic data.

Table 2
Comparative advantages and disadvantages of disease-free survival and overall survival as adjuvant trial end points

	Advantages	Disadvantages
DFS	• Quicker to obtain • Reliable (when central, blinded review determines recurrence)	• Unblinded investigator determination of recurrence subject to bias • Heterogeneity of imaging modalities (± contrast), detection bias possible • May not correlate with OS
OS	• Most relevant outcome for patients and physicians • Easy/reliable to collect and interpret	• May be prohibitively long to reach median survival (10–15 y), preventing expedient trial completion • Patients may lose contact after routine surveillance ends, leading to uncaptured events

ADJUVANT TRIALS OF CLASSIC IMMUNOTHERAPY AGENTS

The poor response of RCC to conventional chemotherapy, radiation, or hormone therapy, along with the discovery of the immune sensitivity of kidney cancer, led to the immunotherapy/cytokine era for advanced and metastatic RCC in the 1980s to 2000s.[30] Cytokine therapy with interferon alfa (IFN-α) and high-dose interleukin-2 (HD IL-2) offered patients with advanced disease at least some hope of a response despite a poor prognosis. Response rates for HD IL-2 in patients with metastatic RCC were 12% to 15%, with a small proportion having complete and durable response (5%–6%).[31–33] The burden of toxicity with HD IL-2, although high, was offset with the chance of a durable cure because more than 80% of complete responders had no evidence of disease at 10 years without additional treatment.[31,34] These impressive responses led HD IL-2 to become the first FDA-approved therapy for RCC. HD IL-2 remained an option at some academic centers in the targeted therapy era for highly select patients (younger, healthier, low metastatic burden); however, with impressive responses with new agents, the role of IL-2 has further diminished.[33]

Cytokines have been explored in the adjuvant setting for high-risk individuals. In a randomized study of 247 postnephrectomy patients, IFN-α2b made no difference in the rate of metastases or OS compared with controls.[35] Messing and colleagues[36] randomized 283 patients with completely resected T3 to T4a and/or node-positive disease to IFN-α or observation. There was no benefit with therapy and perhaps a worse median survival in the treatment arm (5.1 years vs 7.4 years, $P = .09$). Similarly, there was hope for adjuvant HD IL-2 as an adjuvant therapy. The toxicity was high but expected (88% with grade 3/4 toxicity); however, efficacy was poor, with the study being closed at the interim analysis after enrolling 69 patients.[37]

Vaccines were commonly administered in conjunction with cytokines in the 1990s to improve efficacy in the metastatic setting, and were also evaluated in the adjuvant setting. German investigators randomized patients undergoing nephrectomy to 6 monthly intradermal injections of an autologous tumor vaccine versus surveillance.[38] In total, 379 patients were evaluable on the intent-to-treat analysis and a benefit was noted in progression-free survival favoring the vaccine group (hazard ratio [HR], 1.59; $P = .0204$). However, concerns about loss of patients after randomization and the absence of survival benefit prevented this therapy from becoming established as a new treatment standard. Another phase III randomized trial evaluating a different patient-derived vaccine, vitespen, was studied in 818 patients and showed no recurrence-free survival (RFS) benefit.[39] A subgroup analysis suggested some benefit in patients with intermediate-risk features, leading this agent to be approved in Russia as an adjuvant therapy.[40]

ADJUVANT TRIALS OF VASCULAR ENDOTHELIAL GROWTH FACTOR–TARGETED AGENTS

Identification of the genetic basis for RCC in von Hippel-Lindau (VHL) disease led to the discovery that this pathway was also important in sporadic forms of clear cell RCC.[41,42] *VHL* acts as a classic tumor suppressor gene. VHL dysregulation leads to hypoxia inducible factor-α/β accumulation and the transcription of products relating to

angiogenesis, glucose transport, and cell cycle regulation.[43,44] A suite of drugs approved for metastatic RCC block the action of the VEGF tyrosine kinases (eg, sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib).[45] Another overlapping pathway resulting in angiogenesis from hypoxic stress involves mammalian target of rapamycin (mTOR), with 2 FDA-approved drugs for RCC (ie, temsirolimus, everolimus).[46–48]

Based on the positive impact of these therapies in metastatic disease, and the high risk and poor prognosis of recurrent/metastatic RCC, a series of randomized placebo-controlled trials beginning in the mid-2000s sought to evaluate tyrosine kinase inhibitors (TKIs) in the adjuvant setting. However, virtually every trial to date has failed to show an improvement in DFS or OS. A single positive trial, the S-TRAC trial,[4] did show a benefit in DFS, but many investigators believe the potential benefits are insufficient to change the standard of care. These trials are briefly reviewed later, and are summarized in **Table 3**.[3–5,49–52]

ASSURE

The ASSURE trial was the largest trial of adjuvant TKIs for high-risk RCC.[3] The trial compared the use of 1 year of adjuvant sorafenib or sunitinib with placebo (1:1:1) and included individuals with intermediate-high or very-high-risk clear cell or non–clear cell RCC. Given toxicity, a dose reduction became standard for all patients to improve tolerability and adherence.

A total of 647 patients were assigned to sunitinib, 649 to sorafenib, and 647 to placebo. After a median follow-up of 5.8 years, the trial was stopped after sufficient events were reached. The primary outcome of the trial, DFS, was not significantly different between groups, including a subanalysis by histology. Similarly, OS did not significantly differ between groups.[3]

Expected adverse effects were common in the active therapeutic arms, including hypertension, hand-foot syndrome, fatigue, and rash/desquamation. Although the midstudy dose reduction significantly reduced patient discontinuation, grade 3 or worse events were still common after the protocol change.

S-TRAC

S-TRAC was an industry-sponsored trial exploring the effect of adjuvant sunitinib in RCC. In this trial, 615 patients with clear cell RCC were randomized to a year of sunitinib versus placebo after surgical resection.[4] Determination of recurrence was made by both investigator assessment as well as a blinded, independent central radiology review (as opposed to ASSURE, which was only by investigator assessment). In this trial, DFS was significantly improved in the sunitinib arm (6.8 vs 5.6 years; HR, 0.76; 95% confidence interval [CI], 0.59–098), a benefit that stands alone as the only survival benefit seen in any of the adjuvant TKI trials. However, OS was not significantly different between the 2 groups at the time of reporting of 5.4 years median follow-up (deaths in 20.7% vs 20.9% in sunitinib and placebo arms, respectively; HR 1.01). Again, the expected toxicity was common for patients in the sunitinib arm (grade 3 and 4 events in 48.4% and 12.1% for the sunitinib arm vs 15.8% and 3.6% for placebo), as were dose reductions and discontinuations (34.3% and 28.1% vs 2% and 5.6% in the sunitinib and placebo arms, respectively). As a result of the DFS benefit, sunitinib did receive FDA approval for this indication. However, owing to the lack of an OS benefit, and the significant side effect profile, several professional organizations have questioned the merit of sunitinib in this setting, and it seems unlikely to be widely used for this indication.[53,54] In a recent update (at 6.6 and 6.7 years median follow-up), DFS continued to be significantly longer in the sunitinib arm (6.2 vs 4.0 years). However, OS data may need more time to mature because of the limited number of events: 67 (21.7%) and 74 (24.2%) patients in each cohort (HR, 0.92; 95% CI, 0.66–1.28).[55]

EVEREST

The EVEREST trial opened in 2010 and randomized 1545 patients with pT1b or pT2-4 completely resected clear cell or papillary RCC to everolimus or placebo for 1 year.[51] RFS is the primary outcome, with secondary outcomes including OS, toxicity profiles, and quality-of-life measures. Trial accrual has closed and final results are expected October 2021.[51]

PROTECT

PROTECT was an industry-sponsored protocol that randomized 1538 patients with pT2 (high grade) or pT3/pT4, pTxN+ clear cell RCC to 1 year of placebo versus pazopanib after surgery. As with other trials, toxicity was an issue, and the 800-mg starting dose of pazopanib was reduced to 600 mg.[49] A total of 403 patients started in the higher-dose randomization (assigned pazopanib_{800} n = 198 vs placebo n = 205) and 1135 at the lower dose (pazopanib_{600} n = 571 vs placebo n = 564).

The primary end point was not met for the ITT_{600} group (HR, 0.86; 95% CI, 0.70–1.06). However, in both the ITT_{800} and ITT_{all} groups, there was a

Table 3
Phase III adjuvant trials using vascular endothelial growth factor/mammalian target of rapamycin pathway targeting agents

	ASSURE	PROTECT	ARISER	ATLAS	S-TRAC	EVEREST	SORCE
Studies	Haas et al,[3] 2016	Motzer et al,[49] 2017	Chamie et al,[5] 2017	Gross-Goupil et al,[50] 2018	Ravaud et al,[4] 2016	S0931[51]	Elsen et al,[52] 2019
Enrollment Dates	April 2006 to Sept 2010	Dec 2010 to Sept 2013	June 2004 to April 2013	May 2012 to July 2016	Sept 2007 to April 2011	May 2010 to Sept 2016	July 2007 to April 2013
N	1943	1538	864	724	615	1545	1711
Status	Complete	Complete	Complete	Complete	DFS data mature (await OS data)	Active (not recruiting)	Complete
Eligibility Criteria	pT2-pT4 pTxN+ pT1 G3/4	pT3-pT4 pT2 G3/4 pTxN+	pT3-pT4 pTxN+ pT1b-pT2 G3/G4	pT2-pT4 pTxN+	pT3-pT4 pTxN+	pT2-pT4 pTxN+ pT1b G3/G4	Leibovich score 3–11
Risk Group (Risk System)	Intermediate or high (UISS)	Intermediate or high (SSIGN)	High (TNM 2002)	Intermediate or high (UISS)	High (UISS)	Intermediate high or high (not specified)	Intermediate or high (Leibovich)
Histology	Clear cell (79%) Non–clear cell (21%)	Clear cell only	Clear cell only	Clear cell only	Clear cell only	Clear cell Non–clear cell	Clear cell (84%) Non–clear cell (16%)
Control Arm	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Intervention arms	Sunitinib 50 or 37.5 mg daily, 4 wk on, 2 wk off Or Sorafenib 400 or 200 mg twice daily	Pazopanib 600 mg or 800 mg daily	Girentuximab 50 mg ×1, 20 mg weekly	Axitinib 5 mg twice daily	Sunitinib 50 mg 4 wk on, 2 wk off	Everolimus 10 mg daily	Sorafenib 400 mg twice daily for 3 y Or Sorafenib twice daily for 1 y, then placebo for 2 y

Treatment Duration (mo)	12	12	6	12–36	12	12	12–36
Minimum Allowed Dose	Sunitinib 25 mg daily Sorafenib 400 mg every other day	Pazopanib 400 mg daily	No dose reductions	Axitinib 1 mg twice daily	Sunitinib 37.5 mg daily	—	Sorafenib 400 mg daily
Key Efficacy Findings	DFS: HR 1.02, 97.5% CI 0.85–1.23 for sunitinib DFS: HR 0.97, 97.5% CI 0.80–1.17 for sorafenib	ITT_{600}: HR 0.86, 95% CI 0.70–1.06 ITT_{800}: HR 0.69, 95% CI 0.51–0.94 ITT_{all}: HR 0.80, 95% CI 0.68–0.95	DFS: HR 0.97, 95% CI 0.79–1.18 OS: HR 0.99, 95% CI 0.74–1.32	DFS: HR 0.870, 95% CI 0.660–1.147	DFS: HR 0.76, 95% CI 0.59–0.98	Pending	Median DFS not reached for any arm, HR 1.01, 95% CI 0.83–1.23
Trial Conclusion	No benefit for sunitinib or sorafenib	No benefit for pazopanib	No benefit for girentuximab	No benefit for axitinib	DFS benefit for sunitinib, OS data not mature	Pending	No benefit for sorafenib

Abbreviations: CI, confidence interval; TNM, tumor node metastasis.
Data from Refs.[3–5,49–52]

significant improvement in DFS favoring pazopanib at a median follow-up of 47.9 months (ITT_{800} HR, 0.69; 95% CI, 0.51–0.94; and ITT_{all} HR, 0.80; 95% CI, 0.68–0.95). There was no difference in OS at the end of the evaluation period for either dose. Dose reductions and discontinuations were high in both treatment arms. Adverse events were common (98% experienced at least 1) with diarrhea, hypertension, hair color changes, and nausea as the most frequent.

ATLAS

The ATLAS trial was an industry-sponsored trial that randomized patients with predominantly clear cell histology to axitinib 5 mg twice daily or placebo for no less than 1 year and no greater than 3 years.[50] A total of 724 patients in Asia and India were randomized, with independent review committee–assessed DFS as the primary end point. At a preplanned interim analysis after 203 DFS events, the trial was stopped because of futility. Although the trial was negative, a preplanned subgroup analysis of patients at highest risk of recurrence showed a reduction in the risk of DFS events per independent review with an HR 0.735 (95% CI, 0.525–1.028). Dose reductions were required in 56% of the patients receiving axitinib, and more grade 3 and 4 adverse events (61% vs 30%) and discontinuations caused by adverse events (23% vs 11%) were reported for axitinib.

SORCE

The SORCE trial was an industry-sponsored trial enrolling patients with either clear cell or non–clear cell histology and intermediate and high risk of recurrence based on the Leibovich score.[52] Patients were randomized (1:1:1) to placebo, 1 year of sorafenib (followed by 2 years placebo), or 3 years of sorafenib. The investigators observed no differences in DFS or OS in any of the preplanned and prepowered analyses, including all randomized patients, high-risk patients only, and patients with clear cell RCC only. Consistent with other trials, there were high rates of discontinuation because of adverse events from sorafenib, including 24% of patients with grade 3 hand-foot syndrome.

ARISER

An additional adjuvant trial evaluated a monoclonal antibody, girentuximab, which binds to carbonic anhydrase IX (CAIX). CAIX is a cell surface antigen that is highly expressed in most clear cell kidney cancers as a result of dysregulation of *VHL*.[56] Targeting this protein with monoclonal antibodies showed promise in slowing disease progression in phase I/II trials and was thus identified as a potential agent for use in the adjuvant setting.[57] The ARISER trial was a randomized, double-blind, placebo-controlled trial that evaluated girentuximab as an adjuvant therapy in patients with high-risk clear cell RCC.[5] The trial enrolled 864 patients randomized to placebo versus girentuximab for 6 months. The trial found no benefit to girentuximab treatment in DFS or OS, regardless of pathologic group. Adverse events were rare and not significantly different between the treatment and placebo arms. Despite its promise in earlier trials, the negative results of the ARISER trial have, for now, ended further inquiry into CAIX as a viable target for management of high-risk RCC.

SUMMARIZING THE EVIDENCE FOR ADJUVANT TREATMENT WITH TYROSINE KINASE INHIBITORS/MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

The results of the adjuvant TKI trials have been widely analyzed, with particular focus on the possible explanations for why the S-TRAC trial found a DFS benefit, whereas the remaining trials, some of which were larger, did not. Various hypotheses have been proposed to explain the divergent results. One explanation is the heterogeneity of inclusion criteria across the studies. S-TRAC had the most restrictive inclusion criteria for the highest-risk individuals, requiring tumors to be at least pT3, whereas ASSURE and both PROTECT and ATLAS all allowed patients with pT1b high-grade and pT2 tumors, respectively. These lower-risk patients comprised approximately one-third of the patient cohort in the ASSURE trial. The assumption is that the presence of these lower-risk patients may have washed out the treatment effect in the higher-risk patients. This potential explanation was evaluated in a post-hoc subset analysis in the ASSURE trial, in which only a high-risk subset of the ASSURE trial that mirrored those patients in the S-TRAC trial (patients with pT3 or pT4 or N+ disease) were analyzed.[7] Despite limiting to this high-risk subset (which was larger than the S-TRAC cohort), they still failed to find a DFS benefit for sunitinib. ATLAS similarly performed a subset analysis on the highest-risk cohort and did show an improvement in DFS.[50] Another potential explanation attributable to differences in inclusion criteria relates to the decision to include non–clear cell histology in the ASSURE trial (representing 20% of the treatment arm), which may be less susceptible to treatment with a TKI.

Table 4
Adjuvant trials using checkpoint inhibitors

	IMMotion 010	Keynote-564	Checkmate 914[67]	Prosper	Rampart[69]
Study	Uzzo et al,[65] 2017	Choueiri et al,[66] 2018	—	Harshman et al,[68] 2019	—
clinicaltrials.gov Identifier	NCT03024996	NCT03142334	NCT03138512	NCT03055013	NCT03288532
Phase	III	III	III	III	III
Status	Active, not recruiting	Active, not recruiting	Recruiting	Recruiting	Recruiting
Sponsor	Hoffmann-La Roche	Merck	Bristol-Myers Squibb	National Cancer Institute	University College, London
Eligibility Criteria	pT2 G4 pT3a G3-4 pT3b/c/T4 pTxN+ M1[a]	pT2 G4 pT3 pT4 pTxN+ M1[a]	pT2a G3/G4 pT2-pT4 pTxN+	cT2-pT4 cTxN+ M1[a]	Leibovich score 3–11
Estimated Enrollment	778	950	800	805	1750
Estimated Completion Date	April 13, 2024	December 28, 2025	July 7, 2023	November 30, 2023	December 1, 2037
Histology	Clear cell or sarcomatoid	Clear cell[b]	Clear cell[b]	Any	Any[c]
Control Arm	Placebo	Placebo	Placebo	Observation	Observation
Intervention arms	Atezolizumab 1200 mg IV q3 wk	Pembrolizumab 200 mg IV q3 wk	Nivolumab + ipilimumab	Nivolumab: 2 doses neoadjuvant Nivo 240 mg, adjuvant Nivo for 9 mo	Durvalumab 1500 mg q4 wk Or Durvalumab 1500 mg q4 wk + tremelimumab

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Table 4
(*continued*)

	IMMotion 010	Keynote-564	Checkmate 914[67]	Prosper	Rampart[69]
					75 mg on day 1 and week 4
Treatment Duration (mo)	12	12	6	9	12
Key Efficacy End Points	DFS, OS	DFS, OS	DFS, OS	RFS, OS, OS (cc)	DFS, OS

Abbreviations: IV, intravenous; M1, patients with isolated lung, soft tissue, or nodal metastases that have been completely resected or ablated; OS (cc), OS among patients with clear cell; q, every.

[a] M1 disease allowed if oligometastatic, sites can be definitively treated, and patient rendered NED.

[b] Sarcomatoid features allowed.

[c] Oncocytoma, medullary, collecting duct excluded.

Data from Refs.[65–69]

Another possible explanation for result differences were differences in drug exposure between the trials. In all of the trials of TKI, dose reductions were allowed, but the minimum allowed dosages differed between trials. Data from advanced kidney cancer studies with TKIs such as axitinib show that there is variability in drug exposure and higher levels may be associated with improved response.[58] In S-TRAC, many patients remained on sunitinib at 50 mg/d, whereas, in ASSURE, poor tolerability led to the protocol being amended to 37.5 mg/d. Although ASSURE could have been hampered by inadequate drug exposure,[3,59] an additional subset analysis of patients having the highest quartile of sunitinib dose did not show any improvement in outcome. Data from the PROTECT trial also suggest that higher drug exposure leads to better drug efficacy; however, similar to ASSURE, there was dose reduction early on because of tolerability (from 800 to 600 mg of pazopanib).[7]

Based on the S-TRAC data, adjuvant sunitinib was brought for regulatory approval in the United States. The FDA Oncologic Drug Advisory Committee had a split vote (6 to 6) but the agent was approved.[60] Neither The Kidney Cancer Research Network of Canada nor the European Association of Urology support routine use of TKIs in the adjuvant setting,[53,54] and the current NCCN guidelines continue to support enrollment in clinical trials as the preferred management strategy for patients with stage 2 and 3 disease. Given the heterogeneity of findings of the adjuvant TKI trials, as well as the toxicity, there is a general consensus that, although adjuvant sunitinib should be discussed, it is not the standard of care for all patients following nephrectomy.

CHECKPOINT INHIBITION IN THE LOCALIZED DISEASE STATE

Inhibition of immune checkpoint tolerance pathways has been shown to produce durable responses and improve survival in several malignancies in the advanced disease state, including RCC. In kidney cancer, nivolumab was first approved after OS benefit was seen compared with everolimus in the second-line setting.[61] Since then, inhibition of the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has become a central component in the treatment of advanced disease, both as monotherapy in the second-line setting and in combination with cytotoxic T lymphocyte–associated protein 4 (CTLA-4) inhibition (ipilimumab) or with TKI (axitinib) in the first-line setting.[62,63]

Checkpoint inhibition has been shown to augment the immune response, resulting in cytotoxicity to tumor cells. This direct cytotoxicity may ultimately be more effective at eliminating residual microscopic cancer cells compared with VEGF inhibition, which relies on inhibiting angiogenesis, which may not be a critical part of the biology of micrometastases. Checkpoint inhibition is a proven viable adjuvant treatment in other malignancies, such as melanoma, where it has been shown to improve RFS in completely resected melanoma at high risk for recurrence.[64] In RCC, there are several ongoing clinical trials with checkpoint inhibitors used in the adjuvant setting. These trials differ slightly in inclusion criteria, histology, timing of therapy, as well as the specific agents (**Table 4**).[65–69] A classic adjuvant therapy design is used in several trials using PD-1/PD-L1 therapy within the first 8 to 12 weeks after surgery for predominantly clear cell or sarcomatoid-transformed RCC. Agents in these trials include pembrolizumab (NCT03142334), durvalumab (NCT03288532), atezolizumab (NCT03024996), and combination therapy with ipilimumab and nivolumab (NCT03138512). The ipilimumab and nivolumab trial is currently undergoing an amendment to allow a monotherapy nivolumab arm.

Training the immune system to recognize residual cells may require the presence of a significant volume of antigen. Treatment in the neoadjuvant (vs adjuvant) phase may allow greater stimulation and promotion of effective tumor-infiltrating lymphocytes and improved immune response because the primary tumor, and its antigenic targets, remain in place at that time. The PROSPER RCC trial (NCT03055013) is a cooperative group trial evaluating a single dose of nivolumab before surgery followed by classic adjuvant therapy for up to a year.[68] This trial differs from pure adjuvant trials because there is no placebo control, and the single dose given in the neoadjuvant phase allows for initial immune priming.

SUMMARY

For patients who undergo surgery for high-risk, clinically localized kidney cancer, approximately half recur in the 6 years following surgery. Adjuvant therapy has been shown to be an effective treatment strategy in a host of solid tumor types, and has been extensively investigated in kidney cancer. However, despite a large number of trials evaluating agents with known biological activity against kidney cancer, only a single trial has shown a DFS benefit when used as an adjuvant therapy to surgery, and has yet to show a benefit in OS. Although sunitinib is FDA approved for

this indication, given the questionable benefit and substantial toxicity, it is unlikely to be widely used. A variety of monoclonal antibodies targeting checkpoint inhibition pathways are now being investigated in the adjuvant and combination neo/adjuvant setting, and initial results are expected in the next 3 to 5 years. Until an effective adjuvant therapy is developed, risk-adapted observation remains the standard following surgery, and enrollment of patients at high risk for recurrence in clinical trials is strongly encouraged.

DISCLOSURE

The authors have nothing to disclose.

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