

Adjuvant Treatment in Renal Cell Carcinoma

Nazli Dizman, MD, Jacob J. Adashek, BA, JoAnn Hsu, BS, Paulo G. Bergerot, MD, Cristiane D. Bergerot, PhD, and Sumanta K. Pal, MD

The authors except for Mr Adashek are affiliated with the Department of Medical Oncology & Therapeutics Research at the City of Hope Comprehensive Cancer Center in Duarte, California. Dr Dizman is a postdoctoral fellow, Ms Hsu is an associate project manager, Dr P. Bergerot is a postdoctoral fellow, Dr C. Bergerot is a postdoctoral fellow, and Dr Pal is an associate clinical professor. Mr Adashek is a student at Western University of Health Sciences, College of Osteopathic Medicine of the Pacific.

Corresponding author:
Sumanta K. Pal, MD
Department of Medical Oncology & Therapeutics Research
City of Hope Comprehensive Cancer Center
1500 East Duarte Road
Duarte, CA 91010
Tel: (626) 256-4673
Fax: (626) 301-8233
E-mail: spal@coh.org

Keywords

Adjuvant, immunotherapy, renal cell carcinoma, targeted therapy

Abstract: In parallel with advances in the treatment of metastatic renal cell carcinoma (RCC), multiple adjuvant treatments have been tested for RCC. Adjuvant approaches now extend beyond conventional immunotherapies, such as interferon alfa and interleukins, to targeted therapies and immune checkpoint inhibitors. Most treatment approaches before the targeted treatment era did not improve patient outcomes, or study results were mixed. For example, a recent study found that disease-free survival was longer with sunitinib than with placebo in high-risk clear cell RCC, which led to the regulatory approval of sunitinib. However, another large study of adjuvant sunitinib in a slightly different patient population did not confirm these results. Ongoing studies of targeted treatments and immune checkpoint inhibitors may clarify the effectiveness of these agents in the near future. This review presents a comprehensive, chronologic examination of studies addressing adjuvant treatment in RCC, focusing on the key differences between similar approaches. It also discusses the future of adjuvant treatment in RCC.

Introduction

Renal cell carcinoma (RCC) will be diagnosed in an estimated 65,340 persons in the United States in 2018. Approximately two-thirds of patients with newly diagnosed RCC have localized or locally advanced disease, mainly owing to the increased use of imaging.¹ Additionally, the diagnosis at an early stage has become more frequent in recent years.² Therefore, patients with early-stage RCC account for a growing proportion of all patients with newly diagnosed disease. Fortunately, for this group of patients, nephrectomy and ablative therapies are potentially curative approaches.³ However, every patient who has been managed with nephrectomy faces some risk for recurrence and must be monitored carefully. Although no specific predictive marker for recurrence exists, a variety of stratification tools have been developed to classify patients with newly diagnosed RCC based on risk for disease recurrence after nephrectomy and survival.⁴⁻⁶ These tools apply tumor and patient characteristics as well as genomic features.

The most frequently used tools were generated in the beginning of the twenty-first century. The first to be developed, at the Mayo

Clinic, was the stage, size, grade, and necrosis (SSIGN) score, which employs pathologic tumor stage, lymph node status, presence of metastasis, tumor size (≥ 5 or < 5 cm), nuclear grade, and presence of tumor necrosis to estimate recurrence risk.⁷ Later, the same institution presented a modified scoring system, the Leibovich prognosis score, which included metastatic status in the parameters. These 2 nomograms divided patients into low-, intermediate-, and high-risk groups on the basis of metastasis-free survival.⁵ In an effort to account for overall and cancer-specific survival, investigators developed the University of California Los Angeles Integrated Staging System (UISS), which stratified patients according to tumor, node, metastasis (TNM) stage, Fuhrman nuclear grade, and Eastern Cooperative Oncology Group (ECOG) performance status.^{4,8} It is reasonable to assume that nomograms for predicting recurrence are generally compatible with one another. Parameters associated with recurrence risk are similar across multiple studies. However, slight variations among nomograms become more apparent when the use of different nomograms in research studies affects the interpretation of results.

In the setting of metastatic RCC (mRCC), drastic changes have taken place within the last decade. Previously, the management of metastatic disease was limited to conventional immunotherapeutic approaches, such as interleukin 2 (IL-2) and interferon alfa (IFN- α). Initially, molecularly targeted therapies demonstrated a progression-free survival (PFS) benefit over IFN- α and/or placebo in phase 3 studies. These therapies include vascular endothelial growth factor (VEGF)-directed agents, such as sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer), pazopanib (Votrient, Novartis), axitinib (Inlyta, Pfizer), and cabozantinib (Cabometyx, Exelixis), as well as mammalian target of rapamycin (mTOR) inhibitors, such as temsirolimus (Torisel, Pfizer) and everolimus (Afinitor, Novartis).⁹ In addition, the checkpoint inhibitor nivolumab (Opdivo, Bristol-Myers Squibb), a programmed death 1 (PD-1) inhibitor, received regulatory approval on the basis of an overall survival (OS) benefit over everolimus in patients with mRCC previously treated with VEGF inhibitors.¹⁰ Combined checkpoint inhibition is the most recently evaluated approach. The combination of nivolumab and ipilimumab (Yervoy, Bristol-Myers Squibb), an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody, was compared with sunitinib in the CheckMate 214 study (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma). In a treatment-naïve population of patients with mRCC, significantly higher response rates and improved OS were shown with nivolumab plus ipilimumab in intermediate- and poor-risk populations. The

combination is already recommended by the European Association of Urology as a first-line approach for patients with intermediate- or poor-risk RCC.^{11,12} Although the aforementioned developments took place in the metastatic arena, interest is now focused on applying them in the adjuvant setting. This review offers a historical perspective of trials of adjuvant therapy completed in the cytokine and targeted therapy era, and it outlines the design and status of ongoing trials of checkpoint inhibitors in the adjuvant setting.

Studies of Adjuvant Therapy During the Cytokine Era

Before the advent of molecularly targeted therapies, cytokine-based treatments, such as IL-2 and IFN- α , were the standard of care for mRCC.¹³ The overall objective response rate with IL-2 was 14%, with durable responses observed in approximately 10% of patients.¹⁴ The most noteworthy disadvantage of IL-2 was an extensive side effect profile that limited its use to a population of young patients with good performance status and relatively limited disseminated disease. IFN- α was considered the standard-of-care approach to mRCC for clinical purposes on the basis of a retrospective analysis of 6 prospective studies that found an OS of 13 months and a PFS of 4.7 months.¹⁵ The evidence regarding the advantages of cytokine-based treatments in mRCC offered hope of a possible benefit from these treatments in the adjuvant setting as well. However, clinical trials did not demonstrate a benefit from cytokine-based treatments in the adjuvant setting (Table 1).

Earlier studies with IFN- α yielded negative results. In a study by Pizzocaro and colleagues, IFN- α did not improve 5-year disease-free survival (DFS) and OS in comparison with placebo in 247 patients with T2 or T3 RCC. DFS and OS rates were 57% and 66%, respectively, in the IFN- α arm, whereas DFS and OS rates were both 67% in the placebo arm. The difference between the arms was not statistically significant.¹⁶ In a later study, Messing and colleagues tested a similar approach, with observation as the control arm. Their study population comprised a wider range of risk groups. Even though PFS and OS were numerically lower in the IFN- α arm, no statistically significant difference was observed (median PFS and OS with IFN- α were 2.2 and 5.1 years, respectively, and with observation were 3 and 7.4 years, respectively).¹⁷

Similar to the adjuvant approach with IFN- α , the adjuvant approach with IL-2 failed to show benefit. A single course of high-dose IL-2 was compared with observation in a small cohort of 69 patients who had locally advanced (pathologic tumor stage 3b-4 or node positivity) or metastatic disease following metastasectomy. In

Table 1. Studies of Adjuvant Therapy for Renal Cell Carcinoma During the Cytokine Era

Reference	Eligibility	Accrual	Arms	Primary Endpoint	Outcome
Pizzocaro et al ¹⁶	pT2 N1-3 M0 or pT3 N0-3 M0	247	IFN- α -2b	DFS and OS rate at 5 y	DFS rate, 0.57%; OS rate, 66%
			Placebo		DFS rate, 67% ($P=.86$); OS rate, 66% ($P=.11$)
Messing et al ¹⁷	pT1-2 N1-3 M0 or pT3-4 N0-3 M0	283	IFN- α	Median PFS and median OS	PFS, 2.2 y; OS, 5.1 y
			Observation		PFS, 3 y ($P=.3$); OS, 7.4 y ($P=.33$)
Clark et al ¹⁸	pT3b-4 Nx M0, pTx N1-3 M0, or pTx Nx M1	69	IL-2	DFS rate at 2 y	DFS in LA, 53%; DFS in M1, 40%
			Observation		DFS in LA, 48% ($P=.53$); DFS in M1, 67% ($P=.50$)
Atzpodien et al ²⁰	pT3b-4 Nx M0, pTx N1-3 M0, or pTx Nx M1	203	IL-2 + IFN- α + 5-FU	2-y DFS	DFS rate, 48%
			Observation		DFS rate, 55% ($P=.431$)
Aitchison et al ²¹	pT3b-4 N0-3 M0 or pTx N1-2 M0	309	IL-2 + IFN- α + 5-FU	DFS at 3 y	DFS rate, 61.3%
			Observation		DFS rate, 50.4% ($P=.23$)
Passalacqua et al ¹⁹	pT2-3 N0-3 M0	310	IL-2 + IFN- α	DFS rate at 5 y	DFS rate, 73%
			Observation		DFS rate, 73% ($P=.44$)
Wood et al ²³	pT1b-4 N0 M0 or pTx N1-2 M0	818	HSPCC-96	Recurrence rate at 1.9 y	Recurrence rate, 38%
			Observation		Recurrence rate, 40% ($P=.506$)
Chamie et al ²⁵	pT1b-2 N0 M0 (grade 3-4), pT3-4 N0 M0, or pT (any) N1 M0	864	Girentuximab	DFS and OS at 5 y	DFS rate, 53.9%; OS rate, 77.9%
			Observation		DFS rate, 51.6% ($P=.74$); OS, 78.7% ($P=.94$)

DFS, disease-free survival; 5-FU, 5-fluorouracil; HSPCC, heat shock protein-peptide complex; IFN, interferon; IL, interleukin; LA, locally advanced disease; M1, metastatic disease; OS, overall survival; y, year(s).

total, 44 patients had locally advanced disease and 25 patients had metastatic disease that had been completely resected before recruitment. The study was closed earlier than expected after interim analysis revealed that the primary endpoint had not been met despite full accrual.¹⁸

The Italian Oncology Group for Clinical Research presented a study that explored IL-2 in combination with IFN- α in the adjuvant setting. Although this combination was not clinically beneficial, the authors hypothesized that repeated low doses of IL-2 and IFN- α over a 5-year period would stimulate an immune response against recurrence. Although a separation was seen between the PFS curves after 5 years, the difference was not statistically significant.¹⁹ Overall, cytokine-based adjuvant treatment studies that included various applications of IFN- α or IL-2 failed to demonstrate a significant benefit.

Similarly, 2 European studies that randomly assigned patients with localized RCC to either a combination of

IL-2, IFN- α , and 5-fluorouracil or to observation failed to find a benefit in DFS or OS with active treatment.²⁰ Additionally, treatment discontinuation rates were as high as 35% in the intervention arm owing to high toxicity rates.²¹

In addition to the direct application of cytokines such as IL-2 and IFN- α , vaccine-based treatments were used in another novel immune-based approach. Vaccine therapies were investigated in 2 randomized phase 3 adjuvant studies. In a multicenter study conducted in Germany, 558 patients with pathologic tumor stages 2-3b but no node involvement or metastasis received an autologous renal tumor cell vaccine at 4-week intervals following nephrectomy. The intention-to-treat group, which was evaluable for the final analysis of results, consisted of 379 patients. The results demonstrated superiority of the vaccine therapy over observation in regard to PFS. At 5-year and 70-month follow-up, the PFS rates were 77.4% and

72% in the vaccine group and 67.8% and 59.3% in the placebo group, respectively. Thus, the authors concluded that the autologous vaccine had a beneficial effect in the setting of RCC adjuvant treatment.²² However, key points must be taken into account when these results are interpreted. First, the patient characteristics in the 2 arms were not similar owing to an imbalance between the proportions of excluded patients across arms. Specifically, histologic subtypes varied greatly between the arms; the percentage of patients with clear cell histology was 76% in the vaccine arm and 68% in the control arm. Although the results demonstrated the benefits of vaccine therapy over observation, the differences between the arms limit the reliability of these results. In a separate study, vaccination with vitespen (autologous, tumor-derived heat shock protein-peptide complex 96) failed to reach the primary endpoint of PFS improvement after 1.9 years of follow-up and was associated with a recurrence rate of 38% in the vaccine arm vs 40% in the observation arm.²³

Girentuximab, a monoclonal antibody directed against the protein carbonic anhydrase IX (CAIX), was assessed in the setting of RCC adjuvant treatment. The rationale for inhibiting this transmembrane protein was based on upregulation of the *CAIX* gene in RCC cells as a result of a hypoxic environment induced by von Hippel-Lindau gene inactivation. Analysis of the intention-to-treat population was not revealing in terms of DFS or OS; DFS and OS were better in the subpopulation with a CAIX score above 200 than in the group with a CAIX score below 200.²⁴ However, the improvement in outcomes within the subgroup that had a CAIX score above 200 failed to reach statistical significance.²⁵

The results of a comprehensive systematic review and meta-analysis of randomized controlled trials of vaccine therapies, conventional immunotherapies, and chemotherapy regimens indicated that there is no space for immune-based treatments in the setting of RCC adjuvant treatment.²⁶

Results From Adjuvant Studies During the Targeted Therapy Era

The blockade of tumor angiogenesis via inhibition of signaling in the VEGF pathway is the principal mechanism of action of molecularly targeted therapies for mRCC. The discovery of agents directed against angiogenesis resulted in a significant increase in the survival rates of patients with mRCC that eventually led to research on targeted therapies in the setting of RCC adjuvant treatment. Investigators initially tested sunitinib and sorafenib, then pazopanib, axitinib, and everolimus. So far, the ASSURE (sunitinib vs sorafenib vs placebo), S-TRAC (sunitinib vs placebo), and PROTECT (pazopanib vs placebo)

trials have reported results. SORCE (sorafenib vs placebo), ATLAS (axitinib vs placebo), and EVEREST (everolimus vs placebo) have completed accrual, and the results are expected soon.²⁷⁻³²

ASSURE (Sunitinib Malate or Sorafenib Tosylate in Treating Patients With Kidney Cancer That Was Removed By Surgery), which compared sunitinib or sorafenib with a placebo control, was the first adjuvant study to be published. Patients in this study were recruited following nephrectomy if they had high-risk disease, defined as at least T1b G3-4 N0 M0 disease or lymph node invasion, regardless of pathologic tumor stage and grade. A total of 1943 participants were randomly assigned to sunitinib, sorafenib, or placebo, with stratification according to histology (clear cell vs non-clear cell), surgical method (laparoscopic vs open), ECOG performance status (0 vs 1), and recurrence risk (UISS intermediate-high risk vs high risk). When more than two-thirds of the planned accrual had been achieved, an interim analysis showed high rates of drug toxicity and drug discontinuation: 44% and 45% for patients in the sunitinib and sorafenib arms, respectively. Therefore, the study design was revised to decrease the starting dose of sunitinib from 50 mg to 37.5 mg daily (4 weeks on, 2 weeks off) and the starting dose of sorafenib to 400 mg daily for the first 1 or 2 cycles and to allow titration up to full doses if the lower doses were well tolerated. A total of 54 weeks of adjuvant treatment was planned; however, post hoc analysis showed the median duration of treatment with sunitinib or sorafenib to be 48 weeks.²⁷

After a median follow-up of 5.8 years, the 3 arms did not differ in regard to the primary endpoint of DFS: 5.8 years for sunitinib, 6.1 years for sorafenib, and 6.6 years for placebo. Additionally, analysis of the subgroup with clear cell histology did not show a benefit from adjuvant treatment with either sunitinib or sorafenib. Moreover, rates of treatment-related adverse events (AEs) were higher in this study than in earlier studies of sunitinib or sorafenib in mRCC. Grade 3 or higher AEs were seen in 63% of patients in the sunitinib arm, 72% of those in the sorafenib arm, and 25% of those in the placebo arm. Notably, hypertension, fatigue, rash/desquamation, palmar-plantar erythrodysesthesia, and diarrhea were the most frequent grade 3 or higher AEs, with rates of 17%, 17%, 2%, 15%, and 10% in the sunitinib arm and 16%, 7%, 15%, 33%, and 9% in the sorafenib arm, respectively.²⁷

S-TRAC (A Clinical Trial Comparing Efficacy And Safety of Sunitinib Versus Placebo For the Treatment of Patients at High Risk of Recurrent Renal Cell Cancer) was the second trial examining the use of sunitinib as an adjuvant agent. In this study, designed to include patients with locoregional, high-risk, clear cell RCC, participants

were assigned to either sunitinib (50 mg daily, 4 weeks on and 2 weeks off, for 1 year) or placebo. As in the ASSURE trial, high-risk disease was defined according to the UISS system as tumor stage 3 or higher and/or regional lymph node metastasis. After a median follow-up of 5.4 years, a blinded independent central review determined that the median duration of PFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group (hazard ratio [HR], 0.76; 95% CI, 0.59-0.98; $P=.03$). Additionally, the PFS advantage with sunitinib was more significant in the specific subset of patients who had a higher risk for recurrence (pathologic tumor stage 3, undetermined or absent nodal involvement, nuclear grade of at least 2, and ECOG score of at least 1; alternatively, pathologic tumor stage 4, local nodal involvement, or both). In this group, PFS was 6.2 years in the sunitinib arm vs 4 years in the placebo arm (HR, 0.74; 95% CI, 0.55-0.99; $P<.05$). Investigator-determined DFS was also analyzed; results indicated an increase in DFS with sunitinib compared with placebo that failed to reach statistical significance: 6.5 years vs 4.5 years, respectively (HR, 0.81; 95% CI, 0.64-1.02; $P=.08$). Grade 3 or higher AEs were seen in 60% of patients in the sunitinib arm. Diarrhea (3.9%), palmar-plantar erythrodysesthesia (15%), hypertension (7.8%), fatigue (4.2%), and nausea (34.3%) were the most frequent AEs. Although median OS was not reached at the time of the initial analysis, follow-up analysis, performed by Motzer and colleagues, identified 67 deaths in the sunitinib arm vs 74 deaths in the placebo arm.³³ In light of the PFS benefit with sunitinib, the US Food and Drug Administration approved 54 weeks of adjuvant sunitinib, as used in S-TRAC, for high-risk patients following nephrectomy.³⁴ However, the European Medicines Agency discourages the use of adjuvant sunitinib for patients at high risk for disease recurrence.³⁵

Certain discrepancies between the 2 studies are worth mentioning owing to the clinical importance of the controversial results. Several factors contributed to the opposing results, including study characteristics, patient characteristics, and treatment plan. Although both studies adopted the same hypothesis, they differed in methodology. ASSURE was the first and largest study of RCC adjuvant treatment to date, with twice the sample size of S-TRAC. ASSURE was funded by the National Cancer Institute and recruited patients in the United States, whereas S-TRAC was industry-sponsored and included a multicontinental recruitment population. However, a unique feature of S-TRAC is that DFS was analyzed by a blinded independent central review committee as well as by investigators. In ASSURE, the responses were assessed only by investigators, which may have altered the reliability of the results and overestimated benefit.³⁶

The most prominent discrepancy of possible clinical significance was the difference between risk for recurrence in the 2 studies. The risk for recurrence in the ASSURE trial was smaller than the risk for recurrence in S-TRAC. More precisely, the ASSURE trial included patients with T1b and G3-4 tumors, whereas S-TRAC focused on a more specific patient population with T3 or higher tumors. In addition, whereas S-TRAC recruited only patients with clear cell RCC, ASSURE allowed patients with all histologic types. Given our knowledge that clear cell and non-clear cell RCC respond very differently to treatment approaches, the heterogeneity of the histopathologic subtypes included in ASSURE may have had effects that resulted in the negative outcome of the study. Haas and colleagues performed a subgroup analysis of the ASSURE trial in an effort to understand whether the previously listed factors were responsible for the difference between the results in the 2 trials. The subgroup included 1069 patients with clear cell RCC who had pT3, pT4, or node-positive disease. Again, 5-year PFS rates were similar across the sunitinib, sorafenib, and placebo arms (47.7%, 49.9%, and 50.0%, respectively), with no statistically significant difference observed in the 5-year OS rates of the groups.³⁷

The level of exposure to sunitinib was higher in S-TRAC than in ASSURE. As mentioned previously, participants in the ASSURE trial struggled to tolerate sunitinib, and 44% of the population discontinued the drug. Pharmacodynamic and pharmacokinetic studies in patients with mRCC indicated that a higher level of exposure to sunitinib was related to better outcomes, such as longer time to tumor progression and longer OS.³⁸ However, in a subgroup analysis of the ASSURE trial, DFS and OS were assessed according to the quartile of mean sunitinib exposure per 6-week cycle. No correlation with quartile of exposure to either sunitinib or sorafenib was demonstrated for OS and DFS.³⁷

One important lesson to learn from ASSURE and S-TRAC is the importance of standardizing risk groups among studies. As noted previously, currently used stratification systems are based primarily on tumor pathologic characteristics and can vary between investigators. In this new era of precision medicine, the application of genomic or molecular risk stratification is appropriate in the setting of RCC adjuvant treatment. Recently, Rini and colleagues took a step beyond conventional risk stratification strategies by studying the gene signature of clear cell RCC. After 516 genes had been assessed, the investigators used the 16 genes most indicative of recurrence to generate an assay, and stratification by this 16-gene assay was significantly representative of recurrence risk, DFS, disease-specific survival, and OS.⁶ The 16-gene recurrence score was validated in the S-TRAC population to confirm its

reproducibility and reliability.³⁹ However, the assay was identified as prognostic, not predictive, in the context of this study, and the clinical utility of this test has been called into question.

Most recently, in PROTECT (A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma), a randomized phase 3 study of adjuvant pazopanib vs placebo after nephrectomy in patients with localized or locally advanced clear cell RCC, pazopanib failed to demonstrate a survival advantage over placebo. The PROTECT investigators recruited patients whose risk for recurrence was slightly higher than that of the ASSURE population but slightly lower than that of the S-TRAC population. Only patients who had clear cell RCC histology and the following tumor features were included: pT2 (grade 3-4) N0 M0; pT3-4 (any grade) N0 M0; or pT (any) N1 M0. The PROTECT investigators encountered the same dosing toxicity issues as the ASSURE investigators. Because the rates of treatment discontinuation were higher than anticipated, the dose of pazopanib was decreased from 800 to 600 mg daily, and the primary endpoint of the study was modified to examine DFS in the population that received pazopanib at a dose of 600 mg daily. At the end of approximately 3.5 years of follow-up, the primary endpoint was not met in the population treated with 600 mg of pazopanib daily (HR, 0.86; 95% CI, 0.70-1.06; $P=.16$).²⁹

Of note, analysis of the patient population treated with 800 mg of pazopanib ($n=403$) and analysis of the entire study population favored pazopanib over placebo in regard to DFS. Pazopanib at 800 mg daily reduced the relative risk for recurrence or death by 37%. Early and sustained separation of the Kaplan-Meier curves of the group that received pazopanib at 800 mg and the placebo group was apparent. Results suggested a positive correlation between dose and response in the setting of RCC adjuvant treatment. Further assessment of patient blood levels of pazopanib and responses in the PROTECT trial confirmed this correlation. The correlation was independent of dosing, however, which highlights the importance of patient-specific pharmacokinetics.⁴⁰ The side effect profiles of pazopanib at 800 and 600 mg were similar, except for higher rates of hypertension among the patients who received 800 mg. However, the lack of feasibility of pazopanib at 800 mg had already been demonstrated, with a low level of tolerability and high discontinuation rates. Finally, like its predecessors, PROTECT failed to demonstrate an OS benefit with adjuvant pazopanib.

As more agents become available as treatment options for mRCC, they will eventually also be examined in the adjuvant setting. Many trials of adjuvant antiangiogenic agents, including SORCE (Sorafenib in Treating Patients

at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer), EVEREST (Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery), and ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients), have already completed accrual and are expected to provide insight regarding the efficacy of targeted therapies to decrease recurrence.³⁰⁻³² Of the 3 studies, SORCE and ATLAS have a unique component of investigating the duration of adjuvant treatment. Unfortunately, the independent data monitoring committee stopped the ATLAS trial early at the last interim analysis owing to its failure to meet the primary endpoint of DFS. Detailed analysis is forthcoming. If SORCE does not fall victim to amendments owing to intolerable side effects, the results of SORCE and ATLAS have the potential to identify a new roadmap for future study design. Moreover, future study design may quell concerns about the possible limitations of inadequate treatment duration. The most debated question regarding the adjuvant antiangiogenic approach is whether this mechanism of action will be truly effective against micrometastasis. Preclinical animal studies strongly suggest that VEGF inhibition increases micrometastasis formation by blocking vascularization.^{41,42} This may be the reason underlying the lack of benefit derived from using targeted therapies as adjuvant treatment, despite their established role in the metastatic setting.

When all of the dynamics of adjuvant treatment are taken into consideration, the utility of adjuvant targeted therapy is debatable. A large meta-analysis that included all randomized controlled trials in the setting of RCC adjuvant treatment highlighted the fact that adjuvant treatments did not improve OS and were associated with high rates of AEs.⁴³ Gyawali and colleagues conducted an additional meta-analysis for sunitinib and included pooled data from the S-TRAC and ASSURE trials.⁴⁴ Again, results showed no benefit for DFS and potential harm in terms of OS as well as a statistically significant increase in the rate of AEs. The importance of OS should not be overlooked because DFS is not a reliable surrogate for OS in studies of RCC adjuvant treatment.⁴⁵

Adjuvant Studies Beyond the Targeted Therapy Era and Future Directions

Checkpoint inhibitors comprise the third category of adjuvant treatments for localized RCC. Immunotherapies are novel monoclonal antibodies that interfere with the immune escape mechanism of cancer cells and reactivate T cell-mediated immune responses against tumor tissue. Evidence is increasing of the benefits of either single (ie, nivolumab; CheckMate 025 [Study of Nivolumab vs Everolimus in Pre-Treated Advanced or Metastatic

Table 2. Ongoing Trials of Adjuvant Therapy With Immune Checkpoint Inhibitors in Renal Cell Carcinoma

	IMmotion 010 ⁴⁷	KEYNOTE-564 ⁴⁶	PROSPER RCC ⁴⁸	CheckMate 914 ⁴⁹
Sponsor	Industry	Industry	National Cancer Institute	Industry
Design	Adjuvant	Adjuvant	Neoadjuvant + adjuvant	Adjuvant
Comparator and mechanism of action	Atezolizumab PD-L1 inhibition	Pembrolizumab PD-L1 inhibition	Nivolumab PD-1 inhibition	Nivolumab + ipilimumab PD-1 inhibition + CTLA-4 inhibition
Arms	(1) Atezolizumab 1200 mg IV, q3wk for 1 y (2) Placebo 1200 mg IV, q3wk for 1 y	(1) Pembrolizumab 200 mg IV, q3wk for 54 wk (2) Placebo 200 mg IV, q3wk for 54 wk	(1) Nivolumab - neoadjuvant: 240 mg IV, q2wk for 4 wk - adjuvant: 240 mg IV, q2wk for 3 mo then q2wk for 6 mo (2) Standard of care: surgery alone	(1) Nivolumab 3 mg/kg and ipilimumab 1 mg/kg for 24 wk (2) Placebo for 24 wk
Current status	Recruiting	Recruiting	Recruiting	Recruiting
Assessment of outcomes	Investigator and independent review facility	Investigator	Investigator	Independent review facility
Planned accrual	664	950	766	800
Anticipated completion date	2022	2022	2023	2022
Eligibility	T2 (G4) N0 M0 T3a (G3-4) N0 M0 T3b-4 (G any) N0 M0 Tx (G any) N+ M0 M1 no evidence of disease	T2 (G4) N0 M0 T3 (Gx) N0 M0 T4 (G any) N0 M0 Tx (G any), N+ M0 M1 no evidence of disease	T2-4 Nx M0 Tx N1-2 M0	T2a (G3-4) N0 M0 T2b-4 (G any) N0 Tx (G any) N1 M0
Histology	Clear cell with/without sarcomatoid features	Clear cell with/without sarcomatoid features	Any histology	Clear cell with/without sarcomatoid features
Primary endpoint	DFS	DFS	DFS	DFS
Identifier	NCT03024996	NCT03142334	NCT03055013	NCT03138512

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DFS, disease-free survival; G, grade; IV, intravenously; mo, months; PD-1, programmed death 1; PD-L1, programmed death ligand 1; q3wk, every 3 weeks; wk, weeks; y, year.

Clear-cell Renal Cell Carcinoma) or dual (ie, nivolumab plus ipilimumab; CheckMate 214 [A Study Comparing the Combination of Nivolumab and Ipilimumab Versus Placebo in Participants With Localized Renal Cell Carcinoma]) checkpoint inhibition in mRCC.^{10,12} Currently, 4 immunotherapy studies in the adjuvant treatment of localized and advanced RCC are ongoing (Table 2) and are to be completed in approximately 5 years.

Studies of the programmed death ligand 1 (PD-L1) inhibitor atezolizumab (Tecentriq, Genentech) in IMmotion010 and the PD-1 inhibitor pembrolizumab (Keytruda, Merck) in KEYNOTE-564 use similar approaches,

in which patients who have a high recurrence risk following nephrectomy and/or metastasectomy for RCC with clear cell and/or sarcomatoid histology are randomly assigned to 1 year of treatment or placebo.^{46,47} Notably, patients who have undergone metastasectomy are eligible for participation in both studies. In the IMmotion010 trial (A Study of Atezolizumab as Adjuvant Therapy in Participants With Renal Cell Carcinoma at High Risk of Developing Metastasis Following Nephrectomy), an independent review committee will assess patient outcomes. In contrast, in the KEYNOTE-564 trial (Safety and Efficacy Study of Pembrolizumab as Monotherapy in the Adjuvant

Treatment of Renal Cell Carcinoma Post Nephrectomy), the investigators will assess recurrence.

The third immunotherapy agent being assessed in this space is nivolumab. The PROSPER RCC trial (Nivolumab in Treating Patients With Localized Kidney Cancer Undergoing Nephrectomy) has a unique design; it is investigating a neoadjuvant plus adjuvant approach in patients who have clinical stage T2 or higher RCC or any N+ M0 RCC; tumors with any histology are included. Participants in the intervention arm receive 2 doses of nivolumab before nephrectomy and continue treatment with nivolumab for 1 year following nephrectomy; patients in the control arm undergo observation.⁴⁸ Neoadjuvant checkpoint inhibition potentiates dormant antitumor T cells to eradicate both the primary tumor and micrometastases. Thus, a combined neoadjuvant plus adjuvant approach will assess whether early T-cell priming increases the activity and tolerability of adjuvant checkpoint inhibition. If so, this approach has the potential to improve survival, which was not possible with conventional immunotherapies (ie, IL-2).

Dual checkpoint inhibition is being explored in the CheckMate 914 trial (A Study Comparing the Combination of Nivolumab and Ipilimumab Versus Placebo in Participants With Localized Renal Cell Carcinoma) with nivolumab and ipilimumab (3 mg/kg and 1 mg/kg, respectively); patients are randomly assigned to either 6 months of treatment or placebo.⁴⁹ Although immunotherapies are less toxic than targeted therapies, concerns exist about possible toxicities caused by the combination. A study of the adjuvant treatment of melanoma that tested the same combination revealed better DFS, but a significant toxicity profile that was worse than the toxicity profile seen in patients who had metastatic melanoma treated with the same regimen.⁵⁰ In the CheckMate 214 trial, the AE rates were similar in the 2 arms, but treatment was discontinued by 22% of the patients in the combination arm and 12% of the patients in the sunitinib arm. Additionally, in CheckMate 214, there were 7 treatment-related deaths with nivolumab and ipilimumab vs 4 deaths with sunitinib.¹²

Conclusion

As we explore the current data, there is no adjuvant agent with a proven OS benefit. The DFS benefit of sunitinib, in the context of the S-TRAC trial, correlated with the duration of adjuvant treatment, but sunitinib carries a substantial toxicity profile. On the basis of the amalgam of studies available to date assessing the adjuvant use of targeted agents (PROTECT, ASSURE, and S-TRAC), we should delay the adjuvant use of sunitinib at this time. Future work should use not just clinical stratification but

also genomic tools to identify those patients at highest risk for recurrence. Furthermore, multiple trials of immunotherapy are emerging; this approach may be superior to that of adjuvant targeted therapy in terms of toxicity. If the results of these studies are positive, a new standard of care will be established.

Disclosures

Dr Pal has received honoraria from Genentech and is a consultant to Genentech, Aveo, Eisai, Roche, Pfizer, Novartis, Exelixis, Ipsen, Bristol-Myers Squibb, and Astellas. The other authors declare no disclosures.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30.
2. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer*. 2008;113(1):78-83.
3. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney Cancer, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(6):804-834.
4. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol*. 2001;19(6):1649-1657.
5. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer*. 2003;97(7):1663-1671.
6. Rini B, Goddard A, Knezevic D, et al. A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol*. 2015;16(6):676-685.
7. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*. 2002;168(6):2395-2400.
8. Patard JJ, Kim HL, Lam JS, et al. Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *J Clin Oncol*. 2004;22(16):3316-3322.
9. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. *N Engl J Med*. 2017;376(4):354-366.
10. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.
11. Powles T, Albiges L, Staehler M, et al. Updated European Association of Urology Guidelines recommendations for the treatment of first-line metastatic clear cell renal cancer [published online December 7, 2017]. *Eur Urol*. doi:10.1016/j.eururo.2017.11.016.
12. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290.
13. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med*. 2005;353(23):2477-2490.
14. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol*. 1995;13(3):688-696.
15. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon- α as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*. 2002;20(1):289-296.
16. Pizzocaro G, Piva L, Colavita M, et al. Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. *J Clin Oncol*. 2001;19(2):425-431.
17. Messing EM, Manola J, Wilding G, et al; Eastern Cooperative Oncology Group/Intergroup trial. Phase III study of interferon- α -NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. *J Clin Oncol*. 2003;21(7):1214-1222.

18. Clark JI, Atkins MB, Urba WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol*. 2003;21(16):3133-3140.
19. Passalacqua R, Caminiti C, Buti S, et al; POLAR-01 Trial Investigators. Adjuvant low-dose interleukin-2 (IL-2) plus interferon- α (IFN- α) in operable renal cell carcinoma (RCC): a phase III, randomized, multicentre trial of the Italian Oncology Group for Clinical Research (GOIRC). *J Immunother*. 2014;37(9):440-447.
20. Atzpodien J, Schmitt E, Gertenbach U, et al; German Cooperative Renal Carcinoma Chemo-Immunotherapy Trials Group (DGCIN). Adjuvant treatment with interleukin-2- and interferon-alpha2a-based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: results of a prospectively randomised trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). *Br J Cancer*. 2005;92(5):843-846.
21. Aitchison M, Bray CA, Van Poppel H, et al. Adjuvant 5-fluorouracil, alpha-interferon and interleukin-2 versus observation in patients at high risk of recurrence after nephrectomy for renal cell carcinoma: Results of a Phase III randomised European Organisation for Research and Treatment of Cancer (Genito-Urinary Cancers Group)/National Cancer Research Institute trial. *Eur J Cancer*. 2014;50(1):70-77.
22. Jocham D, Richter A, Hoffmann L, et al. Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. *Lancet*. 2004;363(9409):594-599.
23. Wood C, Srivastava P, Bukowski R, et al; C-100-12 RCC Study Group. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet*. 2008;372(9633):145-154.
24. Chamie K, Klopfer P, Bevan P, et al. Carbonic anhydrase-IX score is a novel biomarker that predicts recurrence and survival for high-risk, nonmetastatic renal cell carcinoma: data from the phase III ARISER clinical trial. *Urol Oncol*. 2015;33(5):204.e225-233.
25. Chamie K, Donin NM, Klöpfer P, et al. Adjuvant Weekly Girentuximab Following Nephrectomy for High-Risk Renal Cell Carcinoma: The ARISER Randomized Clinical Trial. *JAMA Oncol*. 2017;3(7):913-920.
26. Scherr AJ, Lima JPS, Sasse EC, Lima CS, Sasse AD. Adjuvant therapy for locally advanced renal cell cancer: a systematic review with meta-analysis. *BMC Cancer*. 2011;11(1):115.
27. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387(10032):2008-2016.
28. Ravaud A, Motzer RJ, Pandha HS, et al; S-TRAC Investigators. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375(23):2246-2254.
29. Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT) [ASCO abstract 4507]. *J Clin Oncol*. 2017;35(15)(suppl).
30. ClinicalTrials.gov. NCT00492258. Sorafenib in treating patients at risk of relapse after undergoing surgery to remove kidney cancer. Identifier: NCT00492258. <https://clinicaltrials.gov/ct2/show/NCT00492258>.
31. ClinicalTrials.gov. Adjuvant axitinib therapy of renal cell cancer in high risk patients (ATLAS). Identifier: NCT01599754. <https://clinicaltrials.gov/ct2/show/NCT01599754>. Accessed June 29, 2018.
32. ClinicalTrials.gov. S0931, everolimus in treating patients with kidney cancer who have undergone surgery (S0931). Identifier: NCT01120249. <https://clinicaltrials.gov/ct2/show/NCT01120249>. Accessed June 29, 2018.
33. Motzer RJ, Ravaud A, Patard JJ, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. *Eur Urol*. 2018;73(1):62-68.
34. FDA approves sunitinib malate for adjuvant treatment of renal cell carcinoma. U.S. Food & Drug Administration. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm585686.htm>. Posted November 16, 2017. Accessed June 29, 2018.
35. Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 19-22 February 2018 (23/02/2018). European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002907.jsp. Posted February 23, 2018. Accessed June 29, 2018.
36. Tang PA, Pond GR, Chen EX. Influence of an independent review committee on assessment of response rate and progression-free survival in phase III clinical trials. *Ann Oncol*. 2010;21(1):19-26.
37. Haas NB, Manola J, Dutcher JP, et al. Adjuvant treatment for high-risk clear cell renal cancer: updated results of a high-risk subset of the assure randomized trial. *JAMA Oncol*. 2017;3(9):1249-1252.
38. Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol*. 2010;66(2):357-371.
39. Escudier BJ, Rini BI, Martini J-F, et al. Phase III trial of adjuvant sunitinib in patients with high-risk renal cell carcinoma (RCC): validation of the 16-gene recurrence score in stage III patients [ASCO abstract 4508]. *J Clin Oncol*. 2017;35(15)(suppl).
40. Sternberg CN, Donskov F, Haas NB, et al. Pazopanib exposure relationship with clinical efficacy and safety in the adjuvant treatment of advanced renal cell carcinoma. *Clin Cancer Res*. 2018.
41. Páez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell*. 2009;15(3):220-231.
42. He S, Lamers GE, Beenakker JW, et al. Neutrophil-mediated experimental metastasis is enhanced by VEGFR inhibition in a zebrafish xenograft model. *J Pathol*. 2012;227(4):431-445.
43. Bai Y, Li S, Jia Z, Ding Y, Gu C, Yang J. Adjuvant therapy for locally advanced renal cell carcinoma: a meta-analysis and systematic review. *Urol Oncol*. 2018;36(2):79.e71-79.e710.
44. Gyawali B, Ando Y. Adjuvant sunitinib for high-risk-resected renal cell carcinoma: a meta-analysis of ASSURE and S-TRAC trials. *Ann Oncol*. 2017;28(4):898-899.
45. Harshman LC, Xie W, Moreira RB, et al. Evaluation of disease-free survival as an intermediate metric of overall survival in patients with localized renal cell carcinoma: A trial-level meta-analysis. *Cancer*. 2017;(Dec):19.
46. ClinicalTrials.gov. Safety and efficacy study of pembrolizumab (MK-3475) as monotherapy in the adjuvant treatment of renal cell carcinoma post nephrectomy (MK-3475-564/KEYNOTE-564). <https://clinicaltrials.gov/ct2/show/NCT03142334>. Identifier: NCT03142334. Accessed June 29, 2018.
47. ClinicalTrials.gov. A study of atezolizumab as adjuvant therapy in participants with renal cell carcinoma (RCC) at high risk of developing metastasis following nephrectomy (IMmotion10). <https://clinicaltrials.gov/ct2/show/NCT03024996>. Identifier: NCT03024996. Accessed June 29, 2018.
48. ClinicalTrials.gov. Nivolumab in treating patients with localized kidney cancer undergoing nephrectomy (PROSPER RCC). <https://clinicaltrials.gov/ct2/show/NCT03055013>. Identifier: NCT03055013. Accessed June 29, 2018.
49. ClinicalTrials.gov. A study comparing the combination of nivolumab and ipilimumab versus placebo in participants with localized renal cell carcinoma (CheckMate 914). <https://clinicaltrials.gov/ct2/show/NCT03138512>. Identifier: NCT03138512. Accessed June 29, 2018.
50. Eroglu Z. Mature results of combination nivolumab (NIVO) plus ipilimumab (IPI) as adjuvant therapy in stage IIIC/IV melanoma (MEL). Presented at: 2017 World Congress of Melanoma; October 18-21, 2017; Brisbane, Australia. Abstract SMR09-6.