Adjuvant Treatment for Renal Cell Carcinoma: Do We Finally Have a Major Breakthrough?

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Abstract: Clinical parameters can be used to identify patients at greatest risk for recurrence following nephrectomy for clinically localized renal cell carcinoma (RCC). Molecular tools are being developed to improve risk stratification. An increasing list of available treatments for metastatic RCC continues to provide hope that an effective adjuvant therapy will be identified for patients with high-risk, clinically localized disease. In a phase 3 adjuvant therapy trial (S-TRAC), sunitinib increased median disease-free survival in patients with clear cell RCC who were at very high risk. This is the first positive phase 3 adjuvant therapy trial using a targeted therapy. However, a much larger phase 3 trial comparing sunitinib, sorafenib, and placebo (ASSURE) was negative. Careful review of recent adjuvant therapy trials reveals insights about who may benefit from adjuvant therapy and provides lessons for future trial design.

Introduction

Approximately 63,000 new cases of kidney cancer occur each year, and the disease causes nearly 14,000 deaths annually.[1] Over the past decade, 2 important developments in renal cell carcinoma (RCC) have prompted the search for adjuvant therapies. First, the US Food and Drug Administration (FDA) approved the use of numerous agents for metastatic RCC (mRCC), which means that established drugs have become available for researchers to evaluate in the adjuvant setting. The targeted therapies that the FDA has approved for use in mRCC include inhibitors of vascular endothelial growth factor (VEGF) signaling and inhibitors of the mammalian target of rapamycin (mTOR). Nivolumab (Opdivo, Bristol-Myers Squibb) has been approved for use in patients with mRCC, and additional checkpoint inhibitors are being evaluated for use in these patients. A recent report suggests that the VEGF receptor–targeted agent sunitinib (Sutent, Pfizer) may be effective as adjuvant therapy. These findings may provide renewed enthusiasm for investigating additional adjuvant and neoadjuvant strategies.[2]

Second, early detection of incidental renal tumors owing to increased use of medical imaging has expanded the opportunity for complete surgical excision and durable cure.[3] Although overall

survival rates have doubled over the past 50 years, from 34% in 1954 to 73% in 2011, the prognosis for high-risk, localized RCC has seen little gain.[4] For example, patients with stage I RCC have a 5-year relapse-free survival rate after surgery of greater than 90%.[5] Unfortunately, 5-year relapse rates after surgical treatment in patients with stage II or III disease are 30% to 40%.[6] Survival after relapse remains poor, and mRCC continues to have the highest mortality rate of the genitourinary cancers.[7]

In this review, adjuvant therapy refers to systemic treatment following surgery for clinically localized cancer. This review discusses strategies for risk stratification to identify candidates for adjuvant treatment. It also discusses ongoing clinical trials and reviews important negative trials in an effort to identify lessons for future trial designs.

Identifying the Risk of Recurrence

The only curative therapy for patients with stage I, II, or III RCC is surgery. Nephrectomy, whether radical or nephron-sparing, is highly effective in removing the primary tumor. Surgery can be performed through a traditional open approach, or via a minimally invasive technique such as laparoscopic or robotic surgery.[8,9] Unfortunately, approximately 20% of patients undergoing potentially curative surgery will relapse.[10] The median time to relapse is 18 months, with the majority of relapses occurring within 2 to 3 years after surgery.[11]

When testing new adjuvant therapies, patients at high risk for recurrence need to be identified. Several clinical nomograms have been developed and validated to identify patients at the highest risk for progression and death after surgery. These systems combine the tumor, node, metastasis (TNM) stage with clinical and pathological features. Adverse prognostic signs include poor performance status; obesity; weight loss; the presence of symptoms; and paraneoplastic syndromes, such as anemia, hypercalcemia, hepatopathy, and thrombocytosis.[12-17] The Leibovich score, which comprises tumor stage, regional lymph node status, tumor size, nuclear grade, and histologic tumor necrosis, has been shown to correlate with progression to metastatic RCC following radical nephrectomy for clear cell RCC.[11] The same team developed another set of prognostic models, called the Mayo Clinic stage, size, grade, and necrosis (SSIGN) scoring system, for predicting site-specific recurrence following curative nephrectomy.[18] In another model that used only clinical variables that were available preoperatively, larger tumor size and the presence of symptoms at presentation were associated with shorter recurrence-free survival.[19] Karakiewicz and colleagues developed a nomogram incorporating TNM stage, tumor size, Fuhrman grade, histologic subtype, local symptoms, age, and sex to predict cancer-specific survival.[20] The University of California Los Angeles Integrated Staging System (UISS) has been validated in localized and metastatic disease for predicting 5-year overall survival. The UISS system uses tumor stage, Fuhrman grade, and Eastern Cooperative Oncology Group (ECOG) performance status to categorize patients as high-, intermediate-, or low-risk.[21]

Molecular profiling and multigene assays have been developed to provide prognostic information beyond traditional histological and clinical factors. Data from the Cancer Genome Atlas have been used to identify various metabolic states of RCC in order to better understand tumor biology and prognosis. For example, upregulation of fatty acid synthesis and pentose phosphate pathway genes was associated with poor survival. Conversely, upregulation of adenosine monophosphate–activated kinase (AMPK), genes involved in the Krebs cycle, and the mTOR pathway was associated with improved survival.[22] More focused efforts to produce a prognostic signature identified 16 genes that predicted the risk of recurrence in a series of 942 patients who had undergone radical nephrectomy for stage I to III clear cell RCC.[23] This gene signature was used to calculate a recurrence score, which was validated in an independent data set to predict tumor recurrence. Although the lack of an effective adjuvant therapy has limited the clinical need for these molecular tools, their use will be justified by the FDA approval of future adjuvant therapies. However, the most compelling argument for using molecular markers will be provided by the development of assays that can identify both patients at high risk for recurrence and patients with tumors that are most likely to respond to a particular systemic therapy. In addition, molecular tests may be a useful part of the inclusion criteria for future clinical trials.

Early Negative Adjuvant Treatment Trials

Some of the early phase 3 trials evaluated radiation and hormonal adjuvant therapies (Table 1). Although radiation is routinely used for brain and painful bone metastases, it has no benefit in the adjuvant setting. A controlled trial evaluated the effect of 50 Gy in 20 fractions to the kidney bed and regional lymph nodes.[24] There was no statistical difference in relapse rates or median survival between the patients who underwent radiotherapy vs those who received no further treatment. Furthermore, in the radiotherapy arm, significant complications occurred in 44% of patients and contributed to death in 19%, resulting in early closure of the trial. This study helped confirm that RCC is a radioresistant tumor. Estrogen and androgen receptors are expressed in 61% and 75% of

Table 1. Early Negative Trials of Adjuvant Treatment With Cytokine Therapy or Cancer Vaccine Therapy

Author, y	Intervention	Patient Population	N	Outcome[a]
Kjaer,[24] 1987	Radiation	Stages II-III	65	**26-mo survival:** 50%
	Observation			**26-mo survival:** 62%
Pizzocaro,[26] 1987	Medroxyprogesterone	All M0	136	**Relapse:** 32.7%
	Observation			**Relapse:** 33.9%
Galligioni,[33] 1996	Tumor cells + BCG	Stages I-III	120	**DFS:** 63%
	Observation			**DFS:** 72%
Pizzocaro,[28] 2001	IFN-α	T3 N0 M0, T2/3N1-3M0	247	**5-y OS:** 66%
	Placebo			**5-y OS:** 66%
Messing,[29] 2003	IFN-α	T3-4a N0-3 M0	283	**Median survival:** 5.1 y
	Observation			**Median survival:** 7.4 y
Clark,[30] 2003	IL-2	T3b-4 N0 M0, T(any) N1-3 M0	44	**2-y DFS:** 53% **2-y OS:** 86%
	Observation			**2-y DFS:** 48% **2-y OS:** 77%
Wood,[35] 2008	HSPPC-96	T1b-T4 N0 M0, T(any) N1-2 M0	819	**Recurrence:** 37.7%
	Observation			**Recurrence:** 39.8%
ARISER,[39] 2015	Girentuximab 50-mg loading dose followed by 20 mg/wk × 23 wk	pT1b-T2 N0 M0 (grade 3-4), pT3-T4 N0 M0, pT(any) N1 M0	864	**DFS:** HR, 0.99; *P*=.74 **OS:** HR, 1.01; *P*=.94 **DFS (high CA9 expression):** HR, 0.55; *P*=.01
	Placebo			

ARISER, Monoclonal Antibody Therapy in Treating Patients Who Have Undergone Surgery for Non-Metastatic Kidney Cancer; BCG, bacillus Calmette-Guérin; CA9, carbonic anhydrase IX; DFS, disease-free survival; HR, hazard ratio; HSPPC-96, autologous tumor–derived heat-shock glycoprotein 96–peptide complex; IFN-α, interferon alfa; IL-2, interleukin 2; mo, month/months; OS, overall survival; TNM, tumor, node, metastasis; wk, week/weeks; y, year/years.

[a] HR comparing treatment and placebo arms.

RCCs, respectively.[25] However, hormonal therapies have been unsuccessful in both the metastatic and adjuvant settings. A prospective randomized multicenter study that compared adjuvant medroxyprogesterone acetate treatment for 1 year vs observation found no difference in relapse rate and no correlations between receptor status, relapses, and treatment.[26]

Negative Adjuvant Treatment Trials With Cytokine and Cancer Vaccine Therapy

Prior to the approval of targeted therapies for mRCC, systemic cytokines were the mainstay of treatment for mRCC.[27] The effectiveness of these agents in mRCC, particularly after cytoreductive nephrectomy and in patients with smaller tumor burden, formed the basis for testing them in the adjuvant setting. Unfortunately, all phase 3 trials that tested systemic cytokines were negative (Table 1). Two adjuvant trials using interferon alfa (IFN-α), as well as one study that used high-dose interleukin 2 (IL-2), showed no improvement in OS or disease-free survival (DFS).[28-30] Combination treatment with IL-2 and IFN-α also failed to improve DFS.[31] Similarly, the combination of cytokines and traditional chemotherapy showed no survival benefit.[32] This trial randomly assigned 309 patients to adjuvant 5-fluorouracil, IFN-α, and IL-2 vs observation and showed no significant benefit of treatment for 5-year OS (70% vs 63%) or DFS (61% vs 50%).

Adjuvant therapy trials of vaccine-based immunotherapies have not produced effective therapies either. Two randomized trials assessed the potential benefit of adjuvant autologous irradiated tumor cells mixed with bacillus Calmette-Guérin. Neither study showed improvement in DFS.[33,34] A study using autologous tumor–derived heat-shock glycoprotein 96–peptide complex (HSPPC-96) showed no significant improvement in DFS.[35] However, one large, multicenter vaccine trial was positive for DFS. In this study, 558 patients from 55 sites in Germany were

randomly assigned to receive intradermal injections of autologous renal tumor cell or no adjuvant treatment.[36] However, this study has been criticized because only 379 patients were assessable owing to histological incompatibility, flawed staging, and loss of follow-up. A planned international phase 3 trial was never performed, and no further development is planned for this treatment.

An antibody-based immunotherapy has been evaluated. Carbonic anhydrase IX (CA9) is a transmembrane protein that is upregulated in clear cell RCC as a result of von Hippel Lindau (*VHL*) gene inactivation. It functions to regulate pH and activate the immune system when released by hypoxic cells.[37,38] A humanized monoclonal antibody targeting CA9 was tested in a phase 3 trial of patients with high-risk RCC.[39] There was no difference in overall survival or DFS between adjuvant treatment and the control treatment. However, a subset analysis showed improved DFS when the tumor had high CA9 expression.[39] This study highlights the potential use of molecular markers for patient selection in adjuvant therapy studies.

Based on these negative studies, it is tempting to dismiss the use of cancer vaccines for RCC. However, it is important to keep in mind that the majority of these trials were designed and completed prior to the development of our modern methods for risk stratification and current understanding of histologic subtypes. Most included non–clear cell histologies that may be less responsive to immune-based treatments, as well as patients with very small tumors and minimal risk for recurrence, effectively underpowering the trials. It is also important to keep in mind that RCC always has been categorized as an immunoresponsive disease, and many lessons learned from recent successes with checkpoint inhibitors in mRCC and adoptive immunotherapies for other solid tumors have yet to be applied and tested in the adjuvant setting for RCC.

Targeted Adjuvant Therapy

The treatment of metastatic RCC has been revolutionized by an improved understanding of the molecular pathophysiology of RCC. In clear cell RCC tumors, biallelic inactivation of the tumor suppressor VHL gene is seen in 80% of cases.[40] Loss of VHL, via mutation, methylation, or chromosome deletion, leads to overaccumulation of the hypoxia-inducible factor (HIF) protein.[41] In addition to the VHL pathway, HIF activity can be stimulated via the mTOR axis.[42] HIF protein acts as a transcription factor leading to expression of hypoxia response elements,[43] including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), CA9, and glucose transporter 1 (GLUT1).

Many of the agents approved or in development for mRCC target the VHL/HIF pathway. The first of these agents approved for mRCC, sorafenib (Nexavar, Bayer), is a small molecule tyrosine kinase inhibitor that targets VEGFR and PDGFR in the endothelium and Raf kinases in the tumor.[44] Other approved agents for mRCC that target these same molecules, albeit with slightly different avidity profiles, include sunitinib (Sutent, Pfizer), axitinib (Inlyta, Pfizer), and pazopanib (Votrient, Novartis).[45,46] Cabozantinib (Cometriq, Exelixis), which is a potent inhibitor of c-MET and VEGFR2, recently was approved as second-line therapy for mRCC.[47] Temsirolimus (Torisel, Pfizer) and everolimus (Afinitor, Novartis) are 2 mTOR inhibitors approved for mRCC.[48] The combination of lenvatinib (Lenvima, Eisai), another multikinase inhibitor targeting VEGFR, and everolimus has been approved for mRCC.[49] Bevacizumab (Avastin, Genentech), a monoclonal blocking antibody for VEGF, is approved for mRCC in combination with INF-α.[50] All of these therapies are potentially effective in the adjuvant setting.

Several large, multicenter phase 3 trials have been reported or are underway evaluating these targeted therapies in the adjuvant setting (Table 2). All of these trials rely on a validated prognostic scoring system for patient selection and evaluate DFS as the primary endpoint. The largest of the adjuvant trials, the ASSURE trial (Sunitinib Malate or Sorafenib Tosylate in Treating Patients With Kidney Cancer That Was Removed by Surgery), randomly assigned 1943 patients with completely resected RCC to sunitinib, sorafenib, or placebo. Patients were stratified based on UISS risk (intermediate-high or very high), clear/non-clear cell histology, ECOG performance status, and resection approach. After accrual of 1322 patients, the starting doses were reduced in response to an unexpectedly high discontinuation rate due to toxicity.[51] The most common adverse effects were hypertension (16%, 16%, 4%), hand-foot reaction (15%, 33%, 1%), rash (2%, 15%, <1%), and fatigue (17%, 7%, 3%) on sunitinib, sorafenib, and placebo, respectively.[51] The final results have been reported, and no significant difference in DFS or OS between any of the study arms was found. Based on these findings, the authors recommended against adjuvant treatment with sorafenib or sunitinib.[51]

However, a similar study known as 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 positive for its primary endpoint, duration of DFS.[2] This international study enrolled 615 patients. A separate Chinese cohort was added after initiation of the trial, but the data were not mature and therefore were not included in the first report. The median duration of DFS was 6.8 years (CI,

Table 2. Completed and Ongoing Targeted Adjuvant Therapy Trials

Trial (Sponsor)	Random-ization	Treatment Details	N	Status	Inclusion Criteria (Stage/Grade)	Inclusion Criteria (Histology)	Results
ASSURE (ECOG)[51]	Sorafenib	400 mg BID × 54 wk Amendment: starting dose reduced to 400 mg daily with dose escalation	1943	Completed	pT1b N0 M0 (grade 3-4), pT2-pT4 N0 M0, pT(any) N1 M0	Any histology[a]	**DFS**: 97.5%; HR, 0.97 (CI, 0.80-1.17) vs placebo
	Sunitinib	50 mg daily (4 wk on/2 wk off) Amendment: starting dose reduced to 37.5 mg daily with dose escalation					**DFS:** 97.5%; HR, 1.02 (CI, 0.85-1.23) vs placebo
S-TRAC (Pfizer)[2]	Sunitinib	50 mg daily (4 wk on/2 wk off), 9 cycles	615	Completed	pT3 N0 M0 (grades 2-4), pT4 N0 M0, pT(any) N1 M0	ccRCC only	**DFS:** 6.8 y vs 5.6 y for placebo; HR, 0.76 (CI, 0.59-0.98; *P*=.03)
ATLAS (Pfizer)	Axitinib	5 mg BID × 3 y	592	Enrolling	pT2-4 N0 M0, pT(any) N1 M0	ccRCC only	
PROTECT (GlaxoSmith-Kline)	Pazopanib	800 mg daily × 1 y Amendment: starting dose reduction to 600 mg daily with dose escalation	1500	In follow-up	pT2 N0 M0 (grades 3-4), pT3-4 N0 M0, pT(any) N1 M0	ccRCC only	
SORCE (Medical Research Council)	Sorafenib	400 mg BID × 1 y or 400 mg BID × 3 y Amendment: starting dose reduction to 400 mg daily in both arms with dose escalation	1420	In follow-up	pT1a N0 M0 (grade 4), pT1b N0 M0 (grades 3-4), pT2-4 N0 M0, pT1b-4 N1 M0	Any histology	
EVEREST (SWOG)	Everolimus	10 mg daily	1218	Enrolling	pT1b N0 M0 (grades 3-4), pT2-4 N0 M0, pT(any) N1 M0	Any histology[a]	

ASSURE, Sunitinib Malate or Sorafenib Tosylate in Treating Patients With Kidney Cancer That Was Removed by Surgery; ATLAS, Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; BID, twice a day; ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival; EVEREST, Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery; HR, hazard ratio; PROTECT, A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma; SORCE, Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer; 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; TNM, tumor, node, metastasis; wk, week/weeks; y, year/years.

[a] duct-Bellini RCC excluded

5.8 to not reached) in the sunitinib arm and 5.6 years (CI, 3.8 to 6.6) in the placebo arm. The median overall survival data were not mature at the time of the first report. The median overall survival, a secondary endpoint, had not been reached in either arm, and the hazard ratio comparing the 2 groups was 1.01 (CI, 0.72-1.44; *P*=.94). In the S-TRAC trial, patients received sunitinib 50 mg per day on a 4-weeks-on, 2-weeks-off schedule for 1 year. Drug-related adverse events were similar to those seen in trials of metastatic disease; however, the treatment discontinuation rate suggests that patients are less tolerant of toxicity after a potentially curative nephrectomy. In S-TRAC, the most common adverse events with sunitinib and placebo, respectively, were diarrhea (57% and 21%), hand-foot reaction (50% and 10%), hypertension (37% and 12%), and fatigue (37% and 24%). Grade 3 or 4 adverse events occurred in 63% of patients in the sunitinib group and 22% of patients in the placebo group. In each arm, 5 patients (1.6%) experienced grade 5 toxicity. The treatment was stopped owing to toxicity in 38% of the sunitinib-treated patients and 6% of the placebo-treated patients. In the sunitinib group, dose reductions occurred in 34% of patients and dose interruptions occurred in 46% of patients.

A close comparison of ASSURE and S-TRAC may provide important insights for treating high-risk RCC and designing future adjuvant therapy trials. There are 4 important differences between ASSURE and S-TRAC that may explain why one study was positive and the other was not. S-TRAC enrolled a higher-risk population than ASSURE. S-TRAC included patients with pT3 and pT4 disease if they were N0M0. However, ASSURE also enrolled patients with pT2 disease and even high-grade pT1b disease if they were N0M0. If only the S-TRAC population benefits from adjuvant therapy, the prediction is that SORCE (Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer; NCT00492258) and EVEREST (Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery; NCT01120249; Table 2) will turn out to be negative trials. ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; NCT01599754) and PROTECT (A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma; NCT01235962) are enrolling patients with risk profiles between ASSURE and S-TRAC.

Another potentially important difference between ASSURE and S-TRAC is that ASSURE included all RCC histologic subtypes, with the exception of collecting duct tumors. However, S-TRAC only enrolled patients with clear cell RCC. It is possible that tyrosine kinase inhibitors that target angiogenesis are most effective for clear cell RCC, and that including non–clear cell histologies effectively underpowered the trial. Another potential explanation accounting for the difference in outcomes for ASSURE and S-TRAC may be related to treatment dose. ASSURE had a high dropout rate due to toxicity. The final dropout rates for the sorafenib and sunitinib arms were 45% and 44%, respectively. The study required an amendment to reduce the starting dose, and allowed for dose escalation. However, with this amendment in place, only 31% of patients in the sorafenib arm and 42% of patients in the sunitinib arm were receiving the highest possible dose at the third cycle. In S-TRAC, patients started at the highest dose and 54% maintained this dose throughout the trial. Patients received more sunitinib in S-TRAC than in ASSURE. Finally, in S-TRAC, disease progression was determined based on central review of imaging. When disease progression was determined by the investigator, the time to progression between the arms was not significantly different. In ASSURE, there was no central imaging review.

Although the S-TRAC results are a major breakthrough for the field, the results are not entirely conclusive. S-TRAC leaves open the possibility that adjuvant sunitinib may simply delay time to recurrence without altering the cure rate. This may become more evident with longer follow-up because the median follow-up was 5.4 years, and RCC can recur even 7 years after nephrectomy. At the time of the first S-TRAC report, the overall survival data were not mature, and overall survival is a secondary endpoint. This is a problem because it leaves open 2 possibilities: (1) Patients treated with adjuvant sunitinib may be less responsive to therapies for metastatic RCC, and therefore have a shorter survival after disease recurrence compared with patients who received placebo; or (2) Patients treated with sunitinib may be at higher risk of death from adverse effects not captured in the trial.

Additional ongoing phase 3 trials that are expected to report their results soon are listed in Table 2. The ATLAS trial is a global multicenter study that is evaluating axitinib 5 mg twice daily as adjuvant therapy for clear cell RCC. In contrast to ASSURE and S-TRAC, which treated patients for a year, ATLAS treats patients for 3 years following nephrectomy. The SORCE trial is directly assessing the importance of treatment duration in a 3-arm study that compares sorafenib for 3 years, sorafenib for 1 year (followed by placebo for 2 years), and placebo. The PROTECT study is evaluating 1 year of pazopanib as adjuvant therapy for clear cell RCC. As in the ASSURE trial, high dropout rates in both SORCE and PROTECT required a midstudy amendment to lower the starting dose. The EVEREST trial from SWOG is exploring adjuvant mTOR inhibitor therapy using everolimus. The inclusion criteria are nearly identical to those for ASSURE.

Challenges in Adjuvant Treatment for RCC

The first challenge is to understand why sunitinib treatment improved DFS in S-TRAC but not in ASSURE. Although the sunitinib dose may be the critical factor, the difference may be related to patient selection or use of central imaging review. A better understanding of the patient population that benefits from adjuvant sunitinib will aid in the design of future clinical trials. The S-TRAC results raise the possibility that many of the past negative trials could have been positive if designed differently. Also related to patient selection, molecular markers should be identified to predict both risk of recurrence and response to therapy. There are several promising molecular signatures that should be tested using tissue collected from large-scale trials of adjuvant therapy. Some of these signatures have already considered tumor heterogeneity during biomarker development, and all future signatures should rely on genes with minimal susceptibility to sampling artifacts.[23,52]

The number of effective therapies for metastatic RCC continues to increase, and we even have an effective combination therapy. These treatments should be considered in the adjuvant setting. However, the number of potentially effective treatments makes this a daunting task. It may finally be time to design neoadjuvant, window-of-opportunity trials that can be used to select the best treatments based on tissue-based endpoints, such as decrease in cellular growth or apoptosis. Only the treatments with the greatest effects seen on surgical specimens can be formally evaluated in phase 3 trials with a DFS endpoint.

ECOG and the Society of Urologic Oncology (SUO) are preparing to evaluate checkpoint inhibitors targeting the programmed death 1 (PD-1)/programmed death–ligand 1 (PD-L1) axis in patients at high risk for recurrence following surgery. ECOG and SUO will need to consider using sunitinib in the control arm. Because sunitinib benefit was seen in high-risk patients identified after surgery, any future neoadjuvant therapy trial may need to allow appropriate patients to receive adjuvant sunitinib. These and other issues will certainly complicate future study design; however, these are minor points in light of the fact that we may be on the verge of a major breakthrough that can produce additional adjuvant and even neoadjuvant therapies.

Conclusion

Clinical and molecular tools are available to identify patients with RCC who are at high risk for recurrence following potentially curative nephrectomy. Despite a long list of phase 3 trials of adjuvant therapies, no adjuvant therapy is commercially available. Much of the recent efforts to identify adjuvant therapies have focused on VEGF-targeted therapies approved for metastatic RCC. In the S-TRAC trial, sunitinib increased DFS in very high-risk patients with clear cell RCC. If this study leads to a new FDA indication for sunitinib, the adjuvant therapy landscape will be permanently altered. A careful review of recent trials will certainly reveal important lessons for the design of future neoadjuvant and adjuvant therapy trials.

Disclosures

The authors have no relevant disclosures.

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