Adjuvant Therapy for Renal Cell Carcinoma: Past, Present, and Future

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ABSTRACT

At the present time, the standard of care for patients who have received nephrectomy for localized renal cell carcinoma (RCC) is radiographic surveillance. With a number of novel targeted agents showing activity in the setting of metastatic RCC, there has been great interest in exploring the potential of the same agents in the adjuvant setting. Herein, we discuss the evolution of adjuvant trials in RCC, spanning from the

immunotherapy era to the targeted therapy era. Pitfalls of current studies are addressed to provide a context for interpreting forthcoming results. Finally, we outline avenues to incorporate promising investigational agents, such as PD-1 (programmed death-1) inhibitors and MNNG transforming gene inhibitors, in future adjuvant trials. *The Oncologist* 2014;19:851–859

Implications for Practice: This work provides an overview of current and ongoing trials of adjuvant (postoperative) therapy for localized renal cell carcinoma. Currently, the gold standard in this disease setting is observation with serial radiographs. The studies we highlight may lead to a dramatic paradigm shift for this disease.

INTRODUCTION

The management of metastatic renal cell carcinoma (mRCC) has evolved dramatically over the past decade. Although cytotoxic agents and immunotherapy previously constituted the primary approach to the disease, multiple targeted agents have now been approved [1]. These agents can broadly be divided into two categories: (a) inhibitors of vascular endothelial growth factor (VEGF) signaling and (b) inhibitors of the mammalian target of rapamycin (mTOR). The first category is constituted by both small molecule VEGF tyrosine kinase inhibitors (VEGF-TKIs), including sunitinib, sorafenib, pazopanib, and axitinib, as well as monoclonal antibodies such as bevacizumab [2–6]. Two mTOR inhibitors are currently approved by the U.S. Food and Drug Administration: temsirolimus and everolimus [7, 8].

Although the availability of seven targeted therapies for mRCC holds promise for patients with the disease, it also prompts several key issues. A question that remains largely unanswered is whether targeted therapies may have a role in the adjuvant setting. Frequently, agents for metastatic cancer have shown benefit when applied after resection of localized cancer. It is hypothesized that this strategy may clear systemic micrometastases. This is perhaps best exemplified in breast cancer, in which several classes of agents have followed a trajectory from the metastatic setting to the adjuvant setting. For instance, endocrine therapies (e.g., tamoxifen and the aromatase inhibitors) first showed activity for

advanced disease but subsequently were shown to delay recurrence in patients who had resection of stage I–III tumors [9–12]. Similarly, targeted therapies applied in HER2-overexpressing or amplified tumors (e.g., trastuzumab) initially demonstrated clinical benefit in the setting of metastatic disease, but studies quickly ensued that demonstrated their benefit as adjuvant [13, 14].

In the setting of renal cell carcinoma (RCC), there have been efforts to characterize the activity of immunotherapeutic agents (e.g., interleukin-2 [IL-2] and interferon- α [IFN- α]) as adjuvant treatment, but as discussed subsequently, these studies have been largely negative. The current review will focus on a series of recently completed and ongoing phase III studies characterizing VEGF- and mTOR-directed agents as adjuvant strategies for RCC with the intent to create a solid platform for future adjuvant design.

ADJUVANT IL-2 AND IFN- α

Prior to the approval of novel targeted agents, IFN- α was used as a reference standard for phase III studies in mRCC [15]. This was on the basis of meta-analytic data suggesting a median time to progression of 4.7 months and a median overall survival (OS) of 13 months. IL-2 was approved for mRCC in 1992, and in comparison with IFN- α , the agent had greater potential for inducing durable responses (occurring in roughly 5–10% of treated patients) [16]. However, use of high-dose IL-2

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has generally been restricted to younger patients with good performance status and more limited metastases.

In the setting of mRCC, phase III studies have shown an improved in OS with the combination of cytoreductive nephrectomy and immunotherapy (as compared with immunotherapy alone) [17]. These studies might allude to the potential for using immunotherapy as an adjunct to surgery for localized disease. However, as noted, the majority of completed adjuvant immunotherapy trials have been negative (Table 1). Pizzocaro et al. [18] randomized 247 patients with pT3a-bN0M0 or pT2/3N1-3M0 RCC to receive either IFN- α (at 6 million international units [MIU] 3 times per week for 6 months) or observation. The primary endpoint of the study was event-free survival at 5 years; ultimately, this was 67.1% in the treatment arm and 56.7% in the control arm ($p = .107$). Furthermore, there was no difference in OS (66.5% in the treatment arm and 66.0% in the control arm; $p = .861$). Of note, subset analyses did reveal a potential benefit with adjuvant IFN- α in those patients with higher risk disease (pN2 versus pN0-1).

A slightly larger study led by the Eastern Cooperative Oncology Group (ECOG) randomized 283 patients with pT3-4aN0M0 or pTxN1-3M0 RCC to similar arms (namely, 6 months of IFN- α or observation) [19]. Dosing of IFN- α varied in this study—specifically, patients received IFN- α for 5 days every 3 weeks at a dose of 3 MIU on day 1, 5 MIU on day 2, and 20 MIU on days 3–5. The study failed to meet the primary endpoint of improving 5-year OS. In fact, 5-year OS was higher in patients treated on the control arm (62% versus 51%; $p = .09$). No significant differences in recurrence-free survival were noted.

A similar lack of success was encountered with studies exploring adjuvant IL-2. A study led by the Cytokine Working Group included patients with locally advanced and metastatic disease that had been completely resected [20]. Locally advanced patients were classified as those with pT3b-4Nx disease or pTxN1-3 disease. Patients were randomized to one cycle of high-dose IL-2 or observation, and the study was powered to show an improvement in 2-year disease-free survival (DFS) from 40% to 70%. Ultimately, the study was closed after enrollment of just 69 patients after an interim analysis suggested futility for the primary endpoint. No difference in OS was seen in this small experience.

Other studies have explored combinations of IL-2 and IFN- α . In the metastatic setting, these studies have shown no substantial benefit over monotherapy [21, 22]. Similar results have been demonstrated in the adjuvant setting. The German Cooperative Renal Carcinoma Chemo-immunotherapy Group conducted a study randomizing patients with pT3b-4N0M0 or pTxN1-3M0 RCC to either 8 weeks of subcutaneous IL-2, subcutaneous IFN- α , and intravenous 5-fluorouracil or observation [23]. With a total of 203 patients enrolled, no DFS benefit was observed with combination therapy, and in fact, OS favored the control arm in this study. The European Organization for the Research and Treatment of Cancer has completed a larger study ($n = 550$) with a similar randomization; this study has completed enrollment, and results are pending [24]. An as-yet-unpublished study from the Italian Oncology Group for Clinical Research randomized 310 patients with pT1-3N1-3M0 RCC to receive subcutaneous IL-2 with subcutaneous IFN- α or no therapy [25]. No significant difference

in 5-year DFS was observed, although DFS curves were noted to diverge to some extent after 5 years. Follow-up data from this trial are eagerly anticipated.

There are several potential reasons why the aforementioned immune-based studies may have produced negative results. First, these treatments may not exert a potent cytotoxic effect. In the case of breast cancer and colorectal cancer, we assume that adjuvant chemotherapy may potentially clear any residual micrometastatic disease. Immune-based treatments may not be as effective in eliminating low-volume disease. Second, these immune-based strategies may have been effective in the setting of clinical or biological enrichment. The former refers to inclusion of higher-risk patients, and the latter refers to inclusion of patients with salient biological factor that predispose to response. These enrichment strategies are discussed in detail later in this work.

VEGF- AND mTOR-DIRECTED THERAPIES IN THE ADJUVANT SETTING

With the excitement and activity of novel targeted agents in the metastatic setting, more recent efforts have focused on transposing these agents into the adjuvant setting. The majority of completed and ongoing trials are examining VEGF-directed agents. In the largest of these studies (ECOG 2805; ASSURE), 1,943 patients with $\geq$ T1bNxM0 disease (Fuhrman grades 3–4) were randomized followed nephrectomy to sunitinib, sorafenib, or placebo for a duration of 1 year [26]. Stratification factors in this study included histology (clear cell versus non-clear cell), performance status (ECOG 0 versus ECOG 1–2), and nature of surgical intervention (open versus laparoscopic). Although the study was originally designed to evaluate full doses of sunitinib and sorafenib, tolerance was poor. As such, midway through the trial, the starting dose was adjusted to sunitinib at 37.5 mg daily (4 weeks on, 2 weeks off) or sorafenib at 400 mg daily for one or two cycles, after which the dose was escalated in the absence of most grade 2 side effects. The primary endpoint of the study is DFS, and data related to DFS and OS are not yet available. However, a cardiac safety study has been reported [27].

Several other studies examining VEGF-directed therapies have similarly completed accrual but have yet to report efficacy data. The S-TRAC study includes 720 patients with high-risk disease ($\geq$ pT2NxM0) based on the UCLA Integrated Staging System (UISS), with randomization to either full dose sunitinib (on a standard schedule) or placebo for a period of 1 year [28, 29]. Notably, this trial did not require a starting dose modification. The SORCE trial, randomized a total of 1,420 patients with intermediate- and high-risk RCC based on the Leibovich criteria (pT1b grades 3–4 or more, NxM0) to either full dose sorafenib for 1 year (followed by placebo for 2 years), sorafenib for 3 years, or placebo for 3 years and also required a starting dose modification, identical to ASSURE midway through the trial to address tolerability [30].

Outside of sunitinib and sorafenib, two other VEGF-directed agents are being explored in the adjuvant setting. The PROTECT study recently completed accrual; in this study, 1,500 patients with pT2N0M0 (Fuhrman grades 3–4), pT3-4N0M0, or pTxN1M0 disease were randomized to 1 year of either full dose pazopanib or placebo [31]. This trial also required a lowering of the starting dose to 600 mg daily for the

Table 1. Randomized trials of adjuvant immunotherapy in RCC

Author [reference]	Experimental arm	Control arm	N	Primary endpoint	Details
Pizzocaro et al. [18]	IFN- α	Observation	247	5-year DFS	<ul style="list-style-type: none"> • Eligibility: pT3-4aN0M0 or pTxN1-3M0 RCC • No difference in 5-year DFS (control: 67.1% vs. IFN-α: 56.7%; $p = .107$) • No difference in 5-year OS (control: 66.5% vs. IFN-α: 66.0%; $p = .861$)
Messing et al. [19]	IFN- α	Observation	283	5-year OS	<ul style="list-style-type: none"> • Eligibility: pT3-4aN0M0 or pTxN1-3M0 RCC • No difference in 5-year DFS (control: 56% vs. IFN-α: 51%; $p = .33$) • No difference in 5-year OS (control: 62% vs. IFN-α: 51%; $p = .09$)
Clark et al. [20]	IL-2	Observation	138	2-year DFS	<ul style="list-style-type: none"> • Eligibility: pT3b-4NxM0 or pTxN1-3M0 or M1 (s/p complete metastasectomy) RCC • No difference in 2-year DFS (control: 55% vs. IL-2: 48%; $p = .431$) • No difference in 2-year OS (control: 86% vs. IL-2: 86%)
Atzpodi en et al. [23]	IL-2/IFN- α /5-FU	Observation	203	2-year DFS	<ul style="list-style-type: none"> • Eligibility: pT3b-4N0M0 or pTxN1-3M0 RCC • No difference in 2-year DFS (control: 62% vs. IL-2/IFN-α/5-FU: 54%) • No difference in 2-year OS (control: 91% vs. IL-2/IFN-α/5-FU: 81%)

Abbreviations: DFS, disease-free survival; 5-FU, 5-fluorouracil; OS, overall survival; s/p, status post.

first one or two cycles for tolerability. The ATLAS study is a smaller effort that will compare axitinib at 5 mg twice daily to placebo in 592 patients with pT2-4N0M0 or pTxN1M0 RCC for a total of 3 years [32]. Only one trial to date is exploring adjuvant therapy with an mTOR inhibitor (EVEREST; SWOG 0931) [33]. In this study, patients with pT1bN0M0 (Fuhrman grades 3–4) or pT2-4N1-3M0 disease are randomized to everolimus or placebo for a period of 1 year. The study has accrued half of a targeted 1,218 patients.

As is readily apparent from Table 2, adjuvant studies of targeted therapies in RCC vary widely in terms of accrual goals, dosing, duration of therapy, and other key characteristics. These characteristics listed above will undoubtedly influence interpretation of the study results, as highlighted subsequently.

OTHER ADJUVANT APPROACHES

Outside of VEGF-TKIs1 and mTOR inhibitors, other targeted approaches have been tested in the adjuvant setting. High expression of carbonic anhydrase IX (CAIX) in clear cell RCC is associated with poor prognosis and may potentially be predictive of clinical outcome in association with specific targeted therapies such as sorafenib [34, 35]. Girentuximab, an antibody to CAIX, was assessed in the phase III ARISER study [36]. Eight hundred and sixty-four patients were stratified into

three risk groups: pT3-4N0M0 disease, pTxN1M0 disease, and pT2bN0M0 or pT2N0M0 (Fuhrman grades 3–4) disease. Patients were randomized to receive a loading dose of girentuximab (50 mg) followed by 23 weekly infusions (20 mg) or placebo. No difference in DFS (hazard ratio [HR], 0.99; $p = .74$) or OS (HR, 1.01; $p = .94$) was seen. However, unplanned subset analyses based on CAIX expression in primary tumor tissue did suggest that those with high CAIX expression did achieve a DFS advantage with girentuximab. A future smaller trial targeting this population could support this approach.

Several other novel approaches have been assessed in the adjuvant setting. Wood et al. [37] examined the use of an adjuvant heat-shock protein peptide complex, HSPPC-96, in 818 patients with high-risk localized RCC (defined as primary tumors larger than 5 cm, positive nodes, or caval involvement). With a median follow-up of approximately 2 years, no difference in DFS was observed (37.7% in the Vitespen group versus 39.8% in the observation group; $p = .506$). More successful results with vaccine therapy were noted in a trial by Jocham et al. [38] in which an autologous tumor cell vaccine generated from primary tumor specimens was examined. A total of 558 patients with pT2-3bN0-3M0 RCC were randomized to receive either six intradermal injections of vaccine or no adjuvant therapy. Ultimately, with 379 evaluable patients for

Table 2. Trials of adjuvant targeted therapy for localized renal cell carcinoma

Trial (sponsor)	Randomization	Duration of therapy (years)	N	Start date	End date ^a	Primary endpoint	Clear cell required?	Details
ASSURE (ECOG)	Sunitinib vs. sorafenib vs. placebo	1	1,943	April 2006	September 2010	DFS	No	<ul style="list-style-type: none"> • Eligibility: pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 RCC • Histology: Any • Cardiac safety substudy reported
ATLAS (Pfizer)	Axitinib vs. placebo	3	592	April 2012	June 2017	DFS	Yes	<ul style="list-style-type: none"> • Eligibility: pT2-4N0M0 or pTxN1M0 RCC
EVEREST (SWOG)	Everolimus vs. placebo	1	1,218	April 2011	October 2021	DFS	No	<ul style="list-style-type: none"> • Eligibility: pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 RCC • Histology: Any • Accrual ~50% complete
PROTECT (GSK)	Pazopanib vs. placebo	1	1,500	November 2010	April 2016	DFS	Yes	<ul style="list-style-type: none"> • Eligibility: pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 RCC
SORCE (MRC)	Sorafenib vs. placebo	3	1,420	June 2007	December 2012	DFS	No	<ul style="list-style-type: none"> • Eligibility: Intermediate- or high-risk RCC (Leibovich score, 3–11)
S-TRAC (Pfizer)	Sunitinib vs. placebo	1	720	July 2007	November 2015	DFS	Yes	<ul style="list-style-type: none"> • Eligibility: High-risk RCC (modified UISS criteria) • pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 RCC

^aStudy completion date reflects estimated primary completion date cited at <http://www.clinicaltrials.gov> or actual date of complete enrollment. Abbreviations: DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; GSK, GlaxoSmithKline; MRC, Medical Research Council; OS, overall survival.

the primary endpoint of DFS, the study was positive; with 5 years of follow-up, the HR for tumor progression was 1.58 (95% confidence interval: 1.05–2.37, $p = .02$), favoring the vaccine group. Certain imbalances in patient characteristics may have potentially contributed to this positive result; for instance, 76% of patients on the vaccine arm had clear cell histology as compared with 68% of patients on the control arm. Across both older immune-based strategies and novel targeted approaches, patients with non-clear cell histologies may be less responsive to treatment as compared to patients with clear cell histology. Furthermore, the trial has been criticized on account of unblinded treatment assignment and a high rate of postrandomization drop-outs. Irrespective of these factors and despite the overall encouraging results from this trial, cost and complexity of manufacturing and distributing the vaccine have foiled the development plan for this autologous vaccine (D. Jocham, personal communication).

A second much smaller trial also explored an autologous tumor cell vaccine. In this study, 120 patients with pT1-3bNXM0 RCC were randomized to receive either no treatment or three intradermal injections of irradiated tumor cells mixed with Bacillus Calmette-Guerin [39]. Although vaccination was able to induce delayed type hypersensitivity reactions in all patients,

it did not result in any benefit in DFS or OS. As discussed subsequently, other vaccines for RCC are currently in development in the metastatic setting (e.g., AGS-003 and IMA-901) [40, 41]. If any of these studies strongly associate a biomarker with clinical outcome, future prospective efforts may enrich for these moieties.

Cytotoxic chemotherapy plays a role in specific subsets of patients with metastatic RCC. For instance, studies have shown some activity of doublet chemotherapy in sarcomatoid mRCC [42]. Furthermore, doublet regimens may play a role in patients with heavily refractory disease [43]. A small prospective study randomized patients with resected Robson stage I or II RCC to either tegafur/uracil or clinical follow-up [44]. At 5-year follow-up, DFS was 80.5% in the group receiving tegafur/uracil, as compared to 77.1% in the group receiving no adjuvant therapy ($p =$ not significant). With more promising targeted therapies in development, it is unclear whether further attention should be devoted to developing adjuvant chemotherapy for RCC.

CHALLENGES FACING THE DESIGN OF ADJUVANT TRIALS

The majority of adjuvant studies described herein have produced negative results despite activity of the therapeutic

agents in the metastatic setting. Although this may be a true reflection of inefficacy for the attempted therapeutic strategy, identification of limitations in adjuvant trial design could lead to more promising advances. One issue to consider is the breadth of tumor-node-metastasis (TNM) stage used in adjuvant trials. The present trials used American Joint Committee on Cancer (AJCC) 2002 TNM classification and the 2010 AJCC classification both refines pT2 into T2a and b but also upstages adrenal involvement from pT3a to pT4. This will further improve risk classification in future trials.

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The postsurgical prognostic nomograms (Leibovich, UISS, and Raj) incorporate performance status and additional histologic features, such as the presence or absence of necrosis into traditional pathologic staging to hone higher risk categories. A challenge in delineating risk is the significant heterogeneity that exists amongst these nomograms for localized RCC. As indicated in Table 3, using a wide spectrum of stage and grade, the risk of recurrence varies widely. For instance, a patient with pT2N0 disease (Fuhrman grade 2) would have a 5-year DFS estimate of 85.4% by the Leibovich nomogram, as compared to 66% by the Kattan nomogram. For a patient with pT3N0 disease (Fuhrman grade 3), the 5-year DFS estimate would be 50% by the Leibovich nomogram, in contrast to 74% by the Kattan nomogram. Several trials use these nomograms to determine eligibility (e.g., SORCE uses the Leibovich score, whereas S-TRAC uses the UISS risk assessment). Eventually, the discordance between these nomograms will have to be accounted for in interpreting study results. Perhaps the foremost example of enrichment based on risk is trials including patients who have received metastasectomy. Although there has never been a randomized study to confirm the benefit of the procedure, single-institution retrospective series suggest 5-year OS estimates as high as 40% [45]. However, the majority of patients do develop disease recurrence, thus underscoring the need for adjuvant therapies in this setting. E2810 is a randomized trial comparing 1 year of full-dose pazopanib therapy or placebo in patients with mRCC that have received complete metastasectomy [46]. Patients will be stratified by disease-free interval (i.e., time from original diagnosis of RCC to the time of metastatic recurrence) and by the number of sites resected. The primary endpoint of the study is 3-year DFS, with the intent of demonstrating an improvement from 25% (with placebo) to 45% (with pazopanib). E2810 is considerably smaller than other adjuvant studies, with an accrual goal of 180 patients. Despite this, the study has suffered from slow accrual to date, possibly because of the relative scarcity of the patient population. Thus, although clinical enrichment for higher risk disease in adjuvant trials may increase the effect size and lessen the required

Table 3. Risk of metastasis by clinical stage using several validated nomograms

Stage	Fuhrman grade	5-year DFS (%)			
		Leibovich	Karakeiwicz	Kattan	Sorbellini
pT2N0	2	89.8	89.2	66	76.9
pT3aN0	2	85.4	84.5	74	86.2
pT3bN0	2	85.4	84.5	56	76.9
pT3cN0	2	85.4	84.5	56	—
pT4N0	2	94.6	81	—	—
pT2N0	4	72.3	74.4	66	20
pT3aN0	4	50	64.8	74	42.3
pT3bN0	4	50	64.8	56	20
pT3cN0	4	50	64.8	56	—
pT4N0	4	74.9	55.2	—	—
pT2N1	2	74.9	79.6		
pT3N1	2	72.3	72.4		
pT4N1	2	85.4	64.8		
pT2N1	4	24.7	51.5		
pT3N1	4	24.7	40.9		
pT4N1	4	50	33.4		

Abbreviations: —, not available; DFS, disease-free survival.

sample size, it comes with the caveat of reducing the proportion of eligible patients. Rapid new drug development and a limited patient population further pressure the need to both conduct and analyze trials quickly.

Additionally, the event rate of recent adjuvant trials, including ARISER, has led to a delay in anticipated outcome reporting. This may be a result of inclusion of earlier stage tumors or better surgical approaches. Statistical design can address some of the recent challenges by incorporating the observed higher event rates seen in recent adjuvant trials such as ARISER and anticipating higher dropout from intolerance or toxicity observed in ASSURE, SORCE, and PROTECT. This will lead to larger trials but with a larger hazard ratio or a defined outcome at 5 years could more rapidly assess novel therapies.

Another confounding variable is the conduct of imaging beyond the 5 years postsurgery. The NCCN guidelines do not recommend imaging follow-up after 5 years; thus the assessment of patients after this period of time can be delayed [47]. Investigators and industry conducting these trials must provide monetary support to conduct regular imaging after this time period; alternatively, one might refine the statistical endpoint to be those events that occur within the first 5 years. The current adjuvant VEGF-TKI trials vary in use of disease-free survival as an endpoint, which include the occurrence of second primary tumors in addition to recurrence of the renal primary or recurrence-free survival, which is limited to the renal primary. Also the premise upon which most modern advanced RCC trials are assessed is progression-free survival as opposed to response rate or overall survival, separating assessment of RCC in both the advanced and adjuvant settings from other breast, colon, and lung cancers. Thus in assessment of VEGF-TKIs, which are generally angiostatic, should the benchmark of benefit in the adjuvant setting be different than

future immunotherapy approaches such as anti-PD-1 (programmed death-1) therapies, in which overall survival may be a more relevant goal?

Outside of schedule, a second issue pertaining to imaging relates to the technologies used. Because 16-slice CT scanners are increasingly replaced with 64- and 128-slice platforms, the threshold for detection of small, recurrent tumors will be lowered. Furthermore, nuclear imaging techniques using biologically relevant radiolabeled antibodies (e.g., ^{124}I -cG250) could either supplant or supplement current imaging modalities and contribute further to this phenomenon. Newer imaging modalities may thusly revise expectations for DFS through a detection bias. Future protocols may also have to account for other subtleties, such as the use of intravenous contrast. As one example, the EVEREST trial initially mandated use of iodinated contrast. Because nephrectomized patients often had compromised creatinine clearance (and could therefore not receive contrast), this requirement had to be revised. However, the nonuse of intravenous contrast may challenge the detection of certain metastatic lesions, such as lymph node recurrences.

Beyond clinical enrichment and statistical modification, a third strategy that might be contemplated is biological enrichment. This approach is more complicated and requires extensive vetting of candidate biomarkers. Ultimately, these biomarkers may be best defined by ongoing studies. For instance, in the context of girentuximab therapy, the level of expression of CAIX (the target of this monoclonal antibody) was associated with DFS [36]. Future studies with girentuximab may thus potentially limit enrollment to individuals with elevated CAIX expression. In the setting of mRCC, multiple biomarkers along the VEGF/mTOR signaling axis have been explored in the context of currently approved therapies [48]. Although results are largely inconsistent, there are opportunities to explore the same moieties in ongoing adjuvant trials. The recently completed ASSURE trial (comparing sunitinib, sorafenib, and placebo) has extensive companion biologic studies. Blood collected from the ASSURE trial will be used to perform assessments of sorafenib pharmacokinetics, circulating DNA, and genome-wide association studies. Tissue will be used to perform assessments of *VHL* mutational status and to create an extensive gene microarray [49].

Furthermore, the high frequency of mutations in epigenetic regulators in RCC may be indicative of tumor behavior. Some such as PBRM1 appear to associate with RCC tumors that also harbor *VHL* mutations but diverge from RCC containing *BAP1* mutations, which may associate with a more aggressive set of pathological characteristics [50–53]. Although these mutations have not yet been characterized with regard to response or resistance to therapy, these data may be hypothesized to be useful in analyzing benefit and/or resistance therapy in the adjuvant and metastatic settings with further pathway correlation and analysis.

INCORPORATING NOVEL AGENTS IN CLINICAL TRIAL DESIGNS

Recently, enthusiasm has been redirected toward modification of immune surveillance. Perhaps the most highly anticipated class of agents are the so-called programmed death-1 (PD-1) and PD-1 ligand (PD-L1) inhibitors [54]. Binding of PD-1 to its ligand (PD-L1 or PD-L2) induces T-cell anergy, and thus

Figure 1. A proposed schema for neoadjuvant/adjuvant clinical trials incorporating PD-1 inhibitors.

Abbreviation: RCC, renal cell carcinoma.

inhibition of the interaction between PD-1 and its ligand perpetuates the antitumor immune response. Nivolumab (BMS-936558; MDX-1106) is the most extensively studied PD-1 inhibitor in mRCC [55]. In an expanded phase I experience, a total of 34 patients with mRCC were treated at varying dose levels [56]. Nearly half (44%) of patients in this cohort had received 3 or more prior therapies. Ten patients exhibited a response (39%), and amongst these responders, the median duration of response was 12.9 months. Notably, even with extended follow-up, no median survival estimate has been reached. These data have resulted in the rapid completion of an international phase III trial comparing everolimus and nivolumab in patients with prior VEGF-directed therapy [57]. Other PD-L1 inhibitors are also currently in development; MPDL3280A is one such agent that has demonstrated encouraging data in a small cohort of patients with RCC [58].

Several adjuvant and neoadjuvant strategies involving PD-1 inhibitors are currently under development. The use of these agents in the adjuvant setting raises important biological questions; for instance, is primary tumor antigen necessary to recruit and propagate T-cell activation in the setting of PD-1 inhibitors? There is preliminary evidence to suggest that resection of renal primary tumors may result in a fall in PD-1-expressing peripheral cells, reducing the putative target for this class of agents (Fig. 1) [59]. Use of neoadjuvant PD-1 inhibition may circumvent this issue, but challenges include administration of a neoadjuvant component, duration of neoadjuvant and/or adjuvant therapy, and whether expression of PD-L1 is necessary for response. One might surmise that this issue could have been important in the aforementioned negative trials exploring IL-2 and IFN- α .

As noted previously, one of the rare positive adjuvant trials in localized RCC evaluated an autologous vaccine-based strategy [38]. Several vaccine-based approaches are in development in the metastatic setting. For instance, the autologous dendritic cell vaccine AGS-003 has been evaluated in combination with sunitinib [41]. In a cohort of 25 patients who had received cytoreductive nephrectomy for mRCC, 21 patients were ultimately treated. Patients enrolled had either intermediate- or poor-risk disease, and in this cohort, an impressive median PFS of 11.9 months was achieved. At the time of last report, median OS had not been achieved despite duration of follow-up in excess of 28 months. Although a phase III study comparing sunitinib with AGS-003 and sunitinib is currently underway for patients with newly diagnosed metastatic disease, one could easily envision using AGS-003 in the adjuvant setting [60]. However, with growing knowledge that agents such as sunitinib may exhibit complex immune effects via modulation of myeloid-derived suppressor cells and regulatory T cells, it is unclear whether AGS-003 as an adjuvant treatment could be offered as monotherapy or whether

concomitant treatment with sunitinib would be required [61]. The same is true for the multi-peptide vaccine IMA901; a phase III study comparing sunitinib with or without this vaccine was recently completed in the metastatic setting [40, 62].

Finally, it may be worthwhile to consider specific adjuvant trials for rare histologies. These trials should be predicated on the biology of each histologic subtype. As one example, one might consider adjuvant trials of MNNG transforming gene (MET)-directed therapies in type 1 papillary RCC, in which aberrant MET expression has been noted. Cabozantinib, a dual inhibitor of VEGFR2 and MET, has shown promising activity in a phase I trial including patients with clear cell RCC, and the agent appears to have preclinical activity in cellular models of papillary RCC (unpublished data) [63]. A comparison of cabozantinib and placebo as adjuvant therapy for papillary RCC would be a challenging undertaking given the relative infrequency of the disease type but would nonetheless fulfill an area of need.

THEORETICAL CONCERNS REGARDING ADJUVANT THERAPY

As summarized by Loges et al. [64] two preclinical data sets heed caution in current efforts to explore VEGF-TKIs in the adjuvant setting. In one report from Pàez-Ribes et al. [65], the RIP1-Tag2 mouse model of pancreatic neuroendocrine tumor was explored. Treatment of localized tumors with an antibody to VEGFR2 resulted in a 4-fold increase in metastases to peripancreatic lymph nodes and a 2-fold increase in metastases to liver, as compared with controls. Treatment with sunitinib yielded similar results. In a simultaneous publication, Ebos et al. [66] used a luciferase-expressing 231/LM2-4 breast cancer cell line. After tail vein injection in SCID mice, metastasis formed more quickly with short-term sunitinib administration (7 days) as compared with vehicle for the same duration. In a distinct set of experiments, tumors were removed from orthotopic 231/LM2-4 xenografts. Treatment with a short duration of sunitinib after resection was observed to increase spontaneous metastasis formation and decrease survival. If these preclinical models are consistent with data yielded from the prospective studies discussed herein, it may be worthwhile to consider similar studies to evaluate other candidates for adjuvant therapy (i.e., PD-1 inhibitors, vaccine therapies, etc.).

A second theoretical challenge to adjuvant therapy may be the increasingly recognized phenomenon of intratumoral heterogeneity. Gerlinger et al. [67] performed an elegant analysis examining tissue from multiple sites of disease in four patients with mRCC. These studies suggested unique genetic aberrations at distinct tumor sites in genes including *SETD2*, *PTEN*, and *KDM5C*. These findings challenge the use of a single targeted therapy abrogating only a selected pathway. In patients who have had resection of localized RCC, sequences or combinations of targeted agents may be necessary to eliminate scattered sites of micrometastasis.

In patients who have had resection of localized RCC, sequences or combinations of targeted agents may be necessary to eliminate scattered sites of micrometastasis.

Figure 2. Schema for PrE0801 (NEXT: Subsequent Exposure to Tyrosine Kinase Inhibition [TKI] at Recurrence After Adjuvant Therapy in RCC).

Abbreviation: RCC, renal cell carcinoma.

CONCLUSION

With several key studies maturing, the fate of adjuvant VEGF-TKI and mTOR inhibitors may be decided within the next several years. If these studies are globally positive, the oncology community will be faced with the challenge of determining which agent to prioritize, paralleling the ongoing debate in the metastatic setting. Furthermore, it will be challenging to ascertain whether front-line therapies for metastatic disease will retain efficacy if patients are challenged with the same agents in the metastatic setting. For instance, should a patient who is exposed to VEGF-TKI as an adjuvant receive another VEGF-TKI at the time of recurrence? The single-arm NEXT trial (PrE0801) was designed to evaluate a total of 105 patients with clear cell RCC who have received sunitinib, sorafenib, pazopanib, or placebo as adjuvant (Fig. 2) [68]. Patients were to receive axitinib on a standard schedule with the primary endpoint of clinical benefit rate, but the study recently closed due to poor accrual. Another possibility is that results from the noted adjuvant trials will be mixed. If there is heterogeneity in results from adjuvant VEGF-TKI and mTOR trials in RCC, careful examination of study designs could offer rationale. If, for instance, treatment with sorafenib for 1 year in ASSURE provides no benefit, whereas treatment for 3 years in SORCE yields a decreased rate of recurrence, one can infer major implications from the duration of therapy. As highlighted in Table 2, there are also key differences in eligibility criteria across these studies. If the baseline characteristics of each study population vary widely, this may certainly have a bearing on study results—and consequently inform which subsets of patients may derive the greatest benefit from adjuvant therapy.

A third and ominous possibility is that all recent adjuvant trials will yield negative results. If this is the case, the onus will be to use the tumor tissue resources obtained from these trials to determine the benefit or lack of benefit from subpopulations and to apply these quickly to the relevant drugs. However, the landscape of therapy for metastatic disease is changing rapidly. As noted, multiple trials of novel immune therapies (PD-1 inhibitors, vaccines, etc.) abound. Certainly, these agents warrant separate evaluation in the adjuvant setting. Drawing upon the previous analogy to breast cancer, in which multiple agents have made a rapid transition into the adjuvant setting, several strategies can be used. First, enriching studies for specific molecular subsets of patients could be a way forward. For instance, in adjuvant trials of trastuzumab, enrollment was limited to patients with HER2-overexpressing or amplified tumors [14]. Second, studies in breast cancer have explored a broad spectrum of therapeutic approaches in the adjuvant setting, with varying durations and sequences of adjuvant treatment. It is possible that alternating VEGF and mTOR inhibition may have merit, akin to sequences of aromatase inhibitors and tamoxifen [69]. Finally, the

statistical design of adjuvant trials in breast cancer could serve as a model in localized RCC. Frequently, the targeted effect size is small, acknowledging the favorable long-term outcomes of breast cancer patients with early stage disease. Trials in RCC may have to use similarly modest goals if low-risk patients (e.g., T1/T2 patients) continue to fall within eligibility parameters. Ultimately, trial designs that incorporate very high-risk categories of patients based on stage and histologic features, succinct statistical design, and molecular refinement would represent a way forward.

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