Integrating Immunotherapy Into the Management of Renal Cell Carcinoma

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Abstract

Before 2005, systemic treatment of metastatic renal cell carcinoma (RCC) was limited to a few minimally effective options. Since then, new agents have emerged targeting the vascular endothelial growth factor and mTOR pathways, which has improved outcomes for patients. Options increased even further beginning in 2015 with 3 new agents, including the addition of nivolumab, the first immune checkpoint inhibitor to demonstrate improved survival in RCC. RCC has long been considered a malignancy with immunogenic potential, and nivolumab offers the potential for durable responses in some patients with a generally tolerable toxicity profile. With so many drugs available to clinicians and patients, properly integrating immune checkpoint blockade (ICB) into the treatment paradigm is challenging. Additionally, emerging research with other ICB agents, as well as ongoing trials of combination strategies, is likely to further impact clinical decision-making. This article attempts to provide some context to inform systemic treatment decisions in the current landscape, with a particular emphasis on the role of immunotherapy, outlines the ongoing immunotherapy research in RCC, and discusses how treatment may evolve.

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The emergence of immunotherapy heralded by drugs targeting immune checkpoints has generated tremendous promise across the oncology community and dramatically altered the therapeutic landscape of many malignancies. Management of renal cell carcinoma (RCC), a cancer long considered “immunogenic,” is a prominent example. In the 1960s, cases of spontaneous remissions in patients with metastatic RCC (mRCC) were reported, documenting a curious phenomenon unique to few metastatic tumors and suggesting an innate ability of the immune system to achieve durable cancer control.^{1–3} In the 1980s and 1990s, interleukin-2 (IL-2) demonstrated the capacity to induce durable remissions in 5% to 7% of patients, albeit with significant toxicity, sparking hope for the possibility of a “cure” in patients considered incurable.^{4,5} Now, immune checkpoint blockade (ICB), with drugs targeting the programmed death 1 (PD-1) pathway, has revolutionized the treatment paradigm and laid the groundwork for further innovation in immunotherapy. Despite this potential,

most patients do not respond to ICB, and no clear biomarkers exist to identify patients most likely to benefit. Thus, strategies to increase response rates and optimize outcomes for patients are needed. This may be achieved in a wide variety of ways, including but not limited to drugs with novel mechanisms, rational combination approaches, and using ICB earlier in the disease trajectory. Fortunately for patients with mRCC, in addition to these new immuno-oncology drugs, novel targeted therapies such as cabozantinib and lenvatinib have recently been approved in the metastatic space. Additionally, the adjuvant space has seen its first positive study, with sunitinib meeting its primary end point of disease-free survival (DFS) versus placebo in patients after curative-intent nephrectomy, but unfortunately with no discernable effect on overall survival (OS) to date.⁶ Without clear evidence-based data from randomized trials to guide practice among the available agents, it can be challenging to decide how best to sequence agents to provide maximal benefit to patients. The Society for

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Immunotherapy of Cancer (SITC) has published a consensus statement from a convened task force of experts in RCC hoping to shed some light on some of the issues surrounding available immuno-oncology drugs.⁷ But this resource currently relies on expert opinion due to the lack of hard evidence. RCC in many ways now suffers from an embarrassment of riches—there are many drugs to choose from, but little guidance on how best to use them. In this article, we attempt to provide some context to inform decisions on how to integrate immunotherapy into the current treatment landscape for RCC based on currently available data, and to hypothesize as to how these new paradigms may evolve.

Treatment of Patients With mRCC

Second-Line and Beyond

Nivolumab, a monoclonal antibody (mAb) targeting PD-1, became the first checkpoint inhibitor to earn FDA approval for treatment of patients with mRCC who had progressed after prior treatment with a tyrosine kinase inhibitor (TKI) by demonstrating improved OS versus everolimus in a phase III trial (CheckMate 025).⁸ Although the overall response rate (ORR) for nivolumab-treated patients in this study was a modest 25%, >30% of these responders achieved durable benefit lasting >12 months. This durability of benefit in responders, the so-called “tail” of the survival curve, underscores the true value of nivolumab, and is graphically more evident in an updated survival curve presented at the 2016 International Kidney Cancer Symposium, which reported 29% of nivolumab responders retained response with a median follow-up of 26 months.⁹ At the time of its approval, second-line options outside of a clinical trial for most patients consisted of either a TKI targeting vascular endothelial growth factor (VEGF) receptor (either axitinib, sorafenib, or TKI of choice not used in the first line between sunitinib/pazopanib) or an mTOR inhibitor (everolimus or temsirolimus). A third mechanistic option, interferon alfa plus bevacizumab, was rarely used.¹⁰ Due to its durability of benefit, nivolumab became the de facto second-line option for most patients with mRCC after progression on a TKI.

Since the approval of nivolumab in TKI-refractory mRCC, both lenvatinib (in combination with everolimus) and cabozantinib have achieved FDA

approval based on randomized data demonstrating improved progression-free survival (PFS), and in the case of cabozantinib, improved OS as well.^{11–13} The availability of these 3 new agents provides new options for patients, but all were tested in the second-line (or beyond) space, and no level 1 data exist comparing them with each other. Within the limitations of cross-trial comparison, one can infer some clues from the available data. All of these contemporary studies tested their drug against a common comparator—everolimus. Both nivolumab and cabozantinib demonstrated an improvement in OS beyond the first-line setting as of December 2016, whereas lenvatinib has exhibited a PFS benefit.^{8,12,13} However, the performance of the control everolimus arm differed somewhat across the studies, likely reflecting subtle differences in the populations. PFS for everolimus was 4.4 months in the CheckMate 025 study,⁸ 3.8 months in the METEOR study¹³ with cabozantinib, and a high of 5.5 months in the lenvatinib/everolimus study.¹² Patients in the lenvatinib study could only have received one prior VEGF-targeted therapy (thus a pure second-line study), which may have contributed to the improved responses because this was a healthier population. Patients in the other 2 studies may have been second or third line, or beyond in the cabozantinib study, which included >25% of patients third line or later, whereas patients in the CheckMate 025 trial could not have been beyond third line. The METEOR trial with cabozantinib also allowed treated brain metastases. Thus, the differing efficacy rates reflect the make-up of the included populations. Data supporting the approval of nivolumab and cabozantinib originate from randomized phase III trials, each with >650 patients, whereas the approval of lenvatinib stems from a randomized phase II study of 153 patients over 3 arms (the combination and each drug alone). Nivolumab was overall well-tolerated, with grade ≥3 treatment-related adverse events (TRAEs) occurring in 19% of patients. Notably, 68% of patients receiving cabozantinib experienced TRAEs grade ≥3. There was one grade 5 AE attributed to cabozantinib, with no AEs attributed to nivolumab, and 60% of patients treated with cabozantinib required a dose reduction. In the combination arm of the lenvatinib/everolimus study, 71% of patients experienced a grade 3/4 TRAE and 24% discontinued treatment due to toxicity. Given the totality of these data, nivolumab appears to be the

preferred option for treatment for most patients with TKI-refractory mRCC (without a contraindication) given its documented OS benefit, potential of a durable response, and favorable toxicity profile.

Still, most patients do not benefit from receiving single-agent nivolumab. Thus, ongoing research is geared toward increasing clinical benefit, with 3 viable options to improve patient outcomes: a better immuno-oncology alternative, a suitable combination approach, or a reliable predictive biomarker to identify who is most likely to benefit (or not benefit). Several other PD-1 pathway inhibitors are being explored in TKI-refractory mRCC. Atezolizumab, a mAb targeting the primary ligand for PD-1 (PD-L1) often found on the tumor cell, was evaluated in a phase IA basket trial including patients with mRCC with both clear cell RCC (ccRCC) and non-clear cell RCC (nccRCC).¹⁴ In patients with ccRCC, the ORR was 15%, with median OS (28.9 months) and toxicity data favorably comparable with nivolumab.

First-Line Metastatic

Current standard of care for first-line treatment of most patients with mRCC is either sunitinib or pazopanib, but for a subset of patients, immunotherapy using high-dose IL-2 (HD IL-2) remains a consideration. In the 2016 consensus statement by the SITC RCC task force, there was a lack of consensus regarding the role of HD IL-2 since the emergence of TKIs and ICB, although two-thirds of members still felt the option should be discussed with all appropriate patients.⁷ HD IL-2 has demonstrated the capacity to provide long-term remissions in a small subset of patients, with approximately 7% attaining a complete response, and approximately 5% alive and disease-free after 65 months.^{4,5,15} Despite this promise, HD IL-2 administration requires in-patient admission and is associated with marked toxicity appropriate only for patients with optimal clinical and physiologic features.⁷ Consequently, HD IL-2 has become increasingly marginalized and is only available to a small subset of healthy patients with ccRCC and access to treatment at high-volume centers.

ICB (generally in combination therapy) as a first-line option is being evaluated in several randomized trials and may further alter the treatment paradigm, affecting downstream second-line options. Efficacy data on single-agent nivolumab as first-line therapy for mRCC is limited, with the largest

published cohort consisting of 24 patients without prior systemic therapy.¹⁶ This group received nivolumab at 10 mg/kg, resulting in 2 complete responses, an ORR of 13%, and a 48-week PFS rate of 39%. These data from a small patient cohort would require further validation, but challenge the long-accepted paradigm that response rates are higher in earlier lines of therapy, and suggest that nivolumab may work better after prior treatment with a TKI, perhaps due to changes to vasculature or tumor antigens occurring in response to VEGF inhibition. Phase III trials of single-agent ICB are not being pursued in the first-line setting.

Combination approaches with ICB are in various stages of clinical testing and are promising potential techniques to increase the percentage of patients who clinically benefit. These approaches are varied and include combined ICB, ICB with a VEGF-targeting TKI, and combining ICB with cytokines or other agents geared to favorably enhance the immune milieu. The goal is to increase efficacy without compromising safety, which so far has proven challenging. Dual checkpoint blockade (ie, adding an agent targeting a separate checkpoint in addition to PD-1) has already garnered approval for improved survival in the first-line treatment of metastatic melanoma using the combination of nivolumab with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-specific mAb ipilimumab. This combination demonstrated improved efficacy over both single agents, but with a consequent increase in grade 3/4 TRAEs.^{14,15} This same combination was initially evaluated in mRCC as part of the CheckMate 016 trial, a multiarm phase I study assessing varying combination doses of nivolumab and ipilimumab for patients with both TKI-refractory and untreated mRCC, with updates last reported at the 2016 ESMO Annual Meeting.¹⁶ Combined data across 2 dose combinations demonstrated an ORR of approximately 40% and a disease control rate close to 80% (complete and partial responses plus stable disease). However, grade 3/4 TRAEs occurred in 38% and 61% of patients, respectively, across the 2 dose combinations reported (nivolumab, 3 mg/kg + ipilimumab, 1 mg/kg, or the opposite). The same CheckMate 016 study also included arms combining nivolumab with sunitinib or pazopanib. Due to increased hepatotoxicity on the TKI arms, both arms were ultimately halted for further study,

dampening enthusiasm for combination PD-1/TKI approaches.¹⁷ However, hope has been renewed with the presentation at ESMO 2016 of the combination of the PD-1 inhibitor pembrolizumab with axitinib, a multitarget TKI approved for treatment of patients with mRCC who have progressed on a prior TKI. Preliminary results showed the combination to be well-tolerated, with grade ≥ 3 immune-related AEs occurring in 19.2% of patients and without significant increases in diarrhea or hepatotoxicity.¹⁸ The ORR was an impressive 71.2%, with a disease control rate of 90.4%. Evidence from combinations of ICB with other therapeutic strategies remains too immature for current discussion.

Because of the impressive efficacy of dual ICB with nivolumab and ipilimumab reported in both the first- and second-line settings, albeit with increased toxicity, a randomized phase III trial of this combination versus sunitinib in previously untreated mRCC patients completed accrual (CheckMate 214; ClinicalTrials.gov identifier: NCT02231749), with results pending.¹⁷ Similarly, based on data presented on axitinib and pembrolizumab, an ongoing phase III trial randomizing this combination against standard sunitinib is currently accruing patients (KEYNOTE-426; ClinicalTrials.gov identifier: NCT02853331). Several other first-line combination trials are also ongoing or planned (Table 1). As a result, although TKIs remain the standard for first-line treatment of mRCC outside of a clinical trial, it is highly likely that combination ICB approaches will achieve regulatory approval within the next few years. The difficulty in choosing optimal therapy may prove to be similar to that for TKI-refractory disease, namely that multiple combinations

could prove to be superior to sunitinib, but data comparing the combinations directly will be lacking, making it challenging for clinicians to differentiate.

(Neo)Adjuvant

Clearly, the role of immunotherapy for patients with mRCC is rapidly evolving, thus the next frontier appears to be determining whether there is a place for ICB in patients with localized disease. The Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) met its primary end point of improving DFS, but without a significant OS benefit to this point; on the heels of the negative results of the adjuvant ASSURE trial (Adjuvant Sorafenib and Sunitinib for Unfavorable Renal Carcinoma), no definitive adjuvant therapy option yet exists.^{6,18} Although we await updated survival analysis from S-TRAC and other unreported adjuvant TKI studies, ICB has entered the clinic in several trials in the adjuvant or neoadjuvant setting. The promise and potential upside is clear: eradicating microscopic residual disease to increase the cure rate after curative-intent surgery. Single-agent PD-1 pathway-targeting drugs have repeatedly been shown to be well-tolerated by most patients, thus it is reasonable to offer them before and after surgery. But as these trials begin to enroll patients, several important issues regarding trial design, clinical rationale, and feasibility are worth considering.

First, whether to administer ICB agents preoperatively, postoperatively, or both in the early disease setting is unclear and controversial. A purely adjuvant study is clean and simple, with patients with high-risk disease recruited after recovery from surgery. This allows for a clear workflow of patients be-

Table 1. Combination Phase III Trials Using Immune Checkpoint Blockade in First-Line Metastatic Renal Cell Carcinoma

ClinicalTrials.gov Identifier	Combination Arms	Control Arm	Primary Outcome
NCT02684006 (JAVELIN Renal 101)	Avelumab + axitinib	Sunitinib	Progression-free survival
NCT02420821	Atezolizumab + bevacizumab	Sunitinib	Progression-free survival and Overall survival (PD-L1–positive patients ONLY)
NCT02853331 (KEYNOTE-426)	Pembrolizumab + axitinib	Sunitinib	Progression-free survival and Overall survival
NCT02811861	Pembrolizumab + lenvatinib OR Lenvatinib + everolimus	Sunitinib	Progression-free survival

ing referred after surgery by urologists to medical oncologists, removing the potential impact of systemic therapy on surgical timing and outcome, and minimizing surgical resistance to referring for preoperative treatments that could delay surgery. However, the efficacy of ICB may prove less relevant in the adjuvant space. Mechanistically, ICB depends on available tumor antigen to be recognized by unleashed immune cells to mount an antitumor response and develop immune memory. Antigen density may be severely limited, or absent, after surgery, limiting efficacy. Additionally, PD-1 expression on peripheral blood mononuclear cells has been shown to dramatically diminish in patients with RCC after nephrectomy, which, for adjuvant therapy, would mean essentially losing the target before firing the first shot.¹⁹ Treating patients preoperatively or perioperatively (ie, both before and after surgery) would allow for antigen recognition when the primary tumor is intact, maximizing immunogenicity. This would also facilitate more meaningful correlative studies, as blood and tissue obtained before starting treatment could be compared with specimens collected at nephrectomy to enhance understanding of changes in the immune milieu and potentiate biomarker exploration. The downside of neoadjuvant treatment is the potential for an autoimmune toxicity that could delay, prevent, or increase the risk of curative-intent surgery.

There are other issues with planning ICB trials in early-stage disease. The selection of the comparator arm in a randomized trial (ie, placebo vs observation) is imprecise. Observation is the current standard, and thus a fair comparator, but bias in investigator assessment of both toxicity and efficacy is inherent in unblinded clinical trials.²⁰ Placebo-controlled trials can mitigate unintended bias, but patient anxiety regarding placebo may limit accrual, and rules regarding unblinding may affect treatment options for patients who develop metastatic disease. Furthermore, as new data from the adjuvant TKI studies become available, the landscape may change, compelling design amendments that could delay and complicate trial analysis, or compel patients to forgo trials to receive sunitinib. Finally, although the side-effect profile of ICB is generally considered tolerable compared with available standard drugs, the appetite for serious AEs changes from the metastatic to curative setting. When treating an incurable disease, patients and clinicians are more willing to

tolerate potentially serious and even fatal AEs. In otherwise healthy patients who may be cured with surgery alone, patients and clinicians may weigh the risks much differently, and this becomes even more relevant when studying dual ICB. Several trials are using ICB in a perioperative setting (Table 2).

Non-Clear Cell RCC

Non-clear cell histologies constitute 20% to 25% of RCCs. However, this group is heterogeneous, and although when grouped together they make up a significant proportion of RCCs, individually each subtype is relatively rare and thus difficult to study in large prospective trials. The most common nccRCC subtype is papillary, but other subtypes include chromophobe, sarcomatoid, collecting duct, medullary, and various hereditary forms. Patients with metastatic nccRCC have generally demonstrated less responsiveness to the drugs shown to be active in ccRCC. In the TKI era, although some patients with nccRCC may derive some benefit from VEGF-targeting TKIs, retrospective studies have generally suggested these agents have inferior efficacy compared with what would be expected in patients with ccRCC.²¹ This was also true in the previous era of immunotherapy, namely with HD IL-2. Although included in some of the larger trials of HD IL-2, patients with nccRCC rarely experienced clinical benefit.^{22–24} Treatment with interferon alfa has also demonstrated limited efficacy in patients with non-clear cell histologies.²⁴ No prospective data currently exist to characterize the response of patients with nccRCC to ICB, though several case reports have been published identifying single responses across various histologies.^{25–27} Several ongoing studies are evaluating ICB as a single agent and in combination in patients with nccRCC.

The Search for Predictive Biomarkers

Despite the initial promise of PD-L1 expression on tumor cells as a reliable biomarker of response, in RCC this appears to have no bearing on whether patients will benefit from treatment, as evidenced by both phase II and III trials of nivolumab in mRCC.^{8,28} Most notably, the negative predictive value (a low or negative PD-L1 expression predicting lack of response from therapy) is poor, thus patients should not be denied ICB based on PD-L1 expres-

Table 2. Perioperative Trials Including Immune Checkpoint Blockade in Renal Cell Carcinoma

ClinicalTrials.gov Identifier	Drugs	Phase	Sponsor	Design	End Points
Pending (PROSPER RCC, EA8143)	Nivolumab	III	ECOG-ACRIN	Randomized to nivolumab for 2 doses before planned nephrectomy, followed by 9 mo adjuvant dosing vs observation	Relapse-free survival
Pending (IMmotion 010, WO39210)	Atezolizumab	III	F. Hoffman-La Roche Ltd.	Randomized to adjuvant atezolizumab for 1 y vs placebo (includes patients with R0 metastasectomy)	Disease-free survival
NCT02575222	Nivolumab	I	Sidney Kimmel Comprehensive Cancer Center	3 doses before planned nephrectomy	Safety
NCT02595918	Nivolumab	Pilot	NCI	3 doses before planned nephrectomy	Feasibility
NCT02212730	Pembrolizumab	I	Merck Sharp & Dohme	3 doses before planned nephrectomy	Safety and intratumoral correlative analyses
NCT02762006	Durvalumab ± tremelimumab	I	Case Comprehensive Cancer Center	Varying dose and schedule combinations of durvalumab alone or with tremelimumab before and after planned nephrectomy	Safety

sion analysis. The reasons for PD-L1 proving to be a poor biomarker have been reviewed extensively and include variables such as tumor heterogeneity, lack of standardization of assays and what denotes a “positive” test, use of archival tissue for testing in trials, and the dynamic nature of PD-L1 expression.²⁹ The most comprehensive assessment of complementary potential biomarkers in mRCC was performed in an exploratory study of nivolumab at varying doses in both treatment-naïve and previously treated patients.¹⁶ Although their findings demonstrated hypothesis-generating changes in tumor-infiltrating lymphocytes and upregulation of interferon γ -associated genes, no clear new biomarkers were identified. Thus, at this time, no reliable predictive model exists, and commercially available PD-L1 assays should not be used to determine who can receive ICB.

Conclusions

Immunotherapy with ICB has established itself in a prominent role in the management of mRCC, with nivolumab leading the way and more drugs and combinations likely to follow. Despite the promise of durable responses with ICB, the field of treatment options for mRCC has become increasingly crowded, leading to uncertainty regarding the optimal place for ICB. It clearly remains a high-priority option for most patients after failure of a first-line TKI, but as the landscape evolves, ongoing trials are likely to establish new roles, possibly in combination, and push ICB earlier in the disease lifecycle. Ample clinical research has begun aiming to define the role of ICB in localized RCC to prevent recurrence, but these trials must proceed with care because results may hinge on appropriate trial design and wholesale patient and clinician buy-in.

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