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Integrating Immunotherapy into the Management of Renal Cell Carcinoma

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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 90s, interleukin-2 (IL-2) demonstrated the capacity to induce durable remissions in 5–7% 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, the majority of patients don’t respond to ICB, and no clear biomarkers exist to identify patients most likely to benefit. Thus, strategies to increase response rates and optimize outcomes in patients are desired. 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 (IO) 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 endpoint of disease-free survival (DFS) versus placebo in patients after curative intent nephrectomy, but unfortunately with no discernable effect on overall survival to date.[6] Without clear evidence-based data from randomized trials to guide practice amongst all of the available agents, it can be challenging to decide how best to sequence agents to provide maximal benefit to patients. The Society for 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 IO 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

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for RCC based on currently available data, and to hypothesize as to how these new paradigms may evolve.

Treatment of Patients with metastatic RCC

2nd line and Beyond

Nivolumab, a monoclonal antibody (mAb) targeting PD-1, became the first checkpoint inhibitor to earn United States Food and Drug Administration (USFDA) approval for treatment of patients with mRCC who had progressed after prior treatment with a tyrosine kinase inhibitor (TKI) by demonstrating improved overall survival (OS) versus everolimus in a phase III trial (CHECKMATE 025).[8] While the overall response rate (ORR) for nivolumab-treated patients in this study was a modest 25%, more than 30% of these responders achieved durable benefit lasting greater than 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 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 1st line between sunitinib/pazopanib) or a mammalian target of rapamycin (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 following progression on a TKI.

Since the approval of nivolumab in TKI-refractory mRCC, both lenvatinib (in combination with everolimus) and cabozantinib have achieved USFDA 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 three new agents provides new options for patients but all were tested in the second line (or beyond) space, and no level one data exists comparing them to 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 1st line setting as of December 2016, while 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. The PFS for everolimus was 4.4 months in the CHECKMATE 025 study, 3.8 months in the METEOR study with cabozantinib, and a high of 5.5 months in the lenvatinib/everolimus study. Patients in the lenvatinib study could only have received one prior VEGF-targeted therapy (thus a pure 2nd-line study) and this may have contributed to the improved responses as this was a healthier population. The patients in the other two studies may have been 2nd or 3rd line, or beyond in the cabozantinib study, which included more than 25% of patients 3rd line or later, while CHECKMATE 025 patients could not have been beyond 3rd 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 from nivolumab and cabozantinib both originate from randomized phase III trials, each with over 650 patients, while 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 or higher 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 adverse event attributed to cabozantinib, with none 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 this 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, the fact remains that the majority of patients do not benefit from receiving single agent nivolumab. Thus, on-going research is geared towards increasing clinical benefit, with three viable options to improve patient outcomes—a better IO 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 mRCC patients with both clear cell RCC (ccRCC) and non-clear cell disease.[14] In the ccRCC patients, the overall response rate (ORR) was 15%, with median OS (28.9 months) and toxicity data favorably comparable with nivolumab. No other PD-1 pathway targeting drugs have reported results as a single agent for refractory mRCC.

1st Line Metastatic

The current standard of care for 1st line treatment of most patients with mRCC is either sunitinib or pazopanib, but for a subset of patients, immunotherapy using high dose interleukin-2 (HD IL-2) remains a consideration. In the 2016 consensus statement by SITC RCC task force, there was a lack of consensus regarding the role of HD IL-2 since the emergence of TKIs and ICB, though 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 about 7% of patients attaining a CR, and about 5% alive and free of disease 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 1st 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 1st 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 two complete

responses (CRs) an ORR of 13%, and a 48 week PFS of 39%. This data from a small patient cohort would require further validation, but challenges the long-accepted paradigm that response rates are higher in earlier lines of therapy, and suggests 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 percent of patients who clinically benefit. These approaches are varied and include combined ICB, ICB with a VEGF-targeting TKI, as well as 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 (i.e. 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 an improvement in efficacy of the combination over either single agent 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 multi-arm, 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 European Society for Medical Oncology (ESMO) Annual Meeting.[16] Combined data across two dose combinations demonstrated an ORR of about 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 two 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 of these arms were ultimately halted for further study, dampening any 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 multi-target TKI approved for treatment of patients with mRCC who have progressed on a prior TKI. Preliminary results of this combination demonstrated the combination to be well tolerated, with grade ≥ 3 immune related adverse events (irAEs) 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.

Due to the impressive efficacy of dual ICB with nivolumab and ipilimumab reported in both the 1st and 2nd 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, NCT02231749), with results pending.[17] Similarly, based on the data presented of axitinib and pembrolizumab, an on-going phase III trial randomizing this combination against standard sunitinib is currently accruing patients (KEYNOTE-426, NCT02853331). Several other 1st line combination trials are also on-going or planned (Table 1). As a result, while TKIs remain the standard for 1st 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 the current state in 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. As noted earlier, the Sunitinib Trial in Adjuvant Renal Cancer (S-TRAC) met its primary endpoint 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 or Sunitinib for Unfavorable Renal Carcinoma), no definitive adjuvant therapy option yet exists.[6, 18] While we await updated survival analysis from S-TRAC and other as yet unreported adjuvant TKI studies, ICB has entered the clinic in several trials in the adjuvant or neoadjuvant space. 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 shown to be well tolerated for most patients, thus it is reasonable to offer to patients before and after surgery. But as these trials begin to enroll patients, there are several important issues in regards to trial design, clinical rationale, and feasibility that are worth considering.

First, the decision on whether to administer ICB agents pre-operatively, post-operatively, or both in the early disease setting is unclear and controversial. A purely adjuvant study is clean and simple, with high risk patients recruited after recovery from surgery. This allows for a clear workflow of patients being 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 pre-operative 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 anti-tumor 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 pre-operatively, or peri-operatively (i.e. 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 prior to starting treatment could be compared to 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 in planning ICB trials in early stage disease. The selection of comparator arm in a randomized trial, placebo versus observation, is imprecise. Observation

is the current standard, thus a fair comparator, but bias in regards to 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, though the side effect profile of ICB is generally considered tolerable compared to 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 by surgery alone, patients and clinicians may weigh the risks much differently, and this becomes even more relevant when studying dual ICB. Several trials are utilizing ICB in a peri-operative setting and are listed in Table 2.

Non-Clear Cell Renal Cell Carcinoma

Non-clear cell (ncc) histologies make up 20–25% of patients with RCC. However, this group is heterogeneous, and while when grouped together they make up a significant proportion of RCC patients, individually each subtype is relatively rare and thus hard 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, while some nccRCC patients may derive some benefit to VEGF-targeting TKIs, retrospective studies have generally suggested inferior efficacy compared to what would be expected in patients with ccRCC.[21] This was true as well in the previous era of immunotherapy, namely with HD IL-2. While included in some of the larger trials of HD-IL2, patients with nccRCC rarely experienced clinical benefit.[22–24] Treatment with interferon-alfa also has demonstrated limited efficacy in patients with non-clear cell histologies.[24] No prospective data exists at this point to characterize the response of patients with nccRCC to immune checkpoint blockade, though there are several case reports that have been published identifying single responses across various histologies.[25–27] Several on-going studies are evaluating immune checkpoint blockade 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 phase 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 expression 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, the use of archival tissue for testing in trials, and the dynamic nature of PD-L1 expression.[29] The most comprehensive study of complementary potential biomarkers in mRCC was assessed in an exploratory study

of nivolumab at varying doses in both treatment naïve and previously treated patients.[16] While their findings demonstrated hypothesis-generating changes in tumor infiltrating lymphocytes (TILs) and upregulation of interferon-gamma 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 1st line TKI, but as the landscape evolves, on-going trials are likely to establish new roles, possibly in combination, and push ICB earlier in the disease life cycle. 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, as results may hinge on appropriate trial design and wholesale patient and clinician buy-in.

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Table 1:

Combination Phase III Trials Utilizing Immune Checkpoint Blockade in 1st Line Metastatic Renal Cell Carcinoma

Clinical Trials Identifier	Combination Arm(s)	Control Arm	Primary Outcome
NCT02684006 (JAVELIN Renal 101)	Avelumab plus Axitinib	Sunitinib	Progression-Free Survival
NCT02420821	Atezolizumab plus Bevacizumab	Sunitinib	Progression-Free Survival And Overall Survival (PD-L1 positive patients ONLY)
NCT02853331 (KEYNOTE-426)	Pembrolizumab plus Axitinib	Sunitinib	Progression-Free Survival And Overall Survival
NCT02811861	Pembrolizumab plus Lenvatinib OR Lenvatinib plus Everolimus	Sunitinib	Progression-Free Survival

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Table 2:

Perioperative Trials Including Immune Checkpoint Blockade in Renal Cell Carcinoma

Clinical Trials Identifier	Drug(s)	Phase	Sponsor	Design	Endpoint(s)
Pending (PROSPER RCC, EA8143)	Nivolumab	III	ECOG-ACRIN	Randomized to nivolumab for 2 doses prior to planned nephrectomy, followed by 9 months adjuvant dosing versus observation	Relapse-Free Survival
Pending (IMmotion 010, WO39210)	Atezolizumab	III	F. Hoffman-La Roche Ltd.	Randomized to adjuvant atezolizumab for 1 year versus placebo (includes R0 metastasectomy patients)	Disease-Free Survival
NCT02575222	Nivolumab	I	Sidney Kimmel Comprehensive Cancer Center	3 doses prior to planned nephrectomy	Safety
NCT02595918	Nivolumab	Pilot	National Cancer Institute	3 doses prior to planned nephrectomy	Feasibility
NCT02212730	Pembrolizumab	I	Merck Sharp & Dohme	3 doses prior to 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

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