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Immune Checkpoint Inhibitors in the Treatment of Renal Cell Carcinoma

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Abstract

Immune checkpoint inhibitors have quickly become a critical component to the management of advanced renal cell carcinoma. These therapies have been approved for patients who are treatment-naïve and who have progressed on anti-angiogenesis agents. Combinations of immune checkpoint inhibitors with anti-angiogenesis agents show significant response rates and prolong survival. Adverse events associated with the use of checkpoint inhibition do present unique challenges in the management of patients, and careful considerations are needed when checkpoint inhibitors are combined with anti-angiogenesis agents. Nevertheless, the improvement in overall survival associated with these agents indicate that they will remain a vital component of treatment of kidney cancer.

Keywords

immunotherapy; checkpoint inhibition; kidney cancer; renal cell carcinoma; immune-related adverse events

INTRODUCTION

The role of immune modulation in renal cell carcinoma (RCC) has long been recognized, since the first descriptions of spontaneous regressions of metastatic RCC (mRCC) after cytoreductive nephrectomy led to the hypothesis that the host immune system could regulate RCC tumor proliferation [1–3]. This eventually led to the development of cytokines such as interleukin-2 (IL-2) and interferon-α (IFN-α) treatment for mRCC [4]. Until 2015, IL-2 was considered an option for fit and young patients with mRCC, based on complete response

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(CR) rates of 5–7% and objective response rates (ORR) of 15–20% [5–7]. Despite the associated toxicity of this regimen, which required hospitalization and management by experienced practitioners, it was a patient's best chance at a sustained disease-free interval.

In the last decade, the role of immune checkpoint blockade in cancer immunotherapy has become better appreciated [8]. Specific T-cell costimulatory molecules, including programmed death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), have been discovered to be negative regulators of antitumor immunity [9]. The host's ability to mount immune responses against cancer cells is restricted by this signaling pathway. While PD-1 is expressed on activated T-cells, PD-L1 is expressed on immune cells and tumor cells. In preclinical studies, the expression of PD-L1 was shown to enhance apoptosis of tumor-specific T cells and to impair T cell function [10,11]. In particular, expression of PD-L1 in the tumors of patients with RCC is associated with an adverse prognosis [12].

Given the observations that RCC can influence or mute native T-cell responses, and in light of the data amassed specifically with PD-1, PD-L1 and CTLA4, antibodies against these targets have been developed and studied in patients with mRCC. In fact, these antibodies have changed the treatment paradigm, as most patients with newly diagnosed mRCC are now treated with checkpoint inhibitor therapy. In this review, we detail the key clinical data supporting the use of checkpoint inhibitors, either alone or in combination with other agents, in the treatment of mRCC. We also review an important facet of immune checkpoint inhibition: the management of toxicities associated with these drugs. Finally, we outline the data to date regarding the role of predictive markers in identifying those who respond to checkpoint inhibitor therapy. While the majority of this review focuses on the most common subtype of RCC, clear cell RCC (ccRCC), we briefly discuss the limited data on the use of immune checkpoint inhibition in patients with non-clear cell RCC (nccRCC).

SINGLE AGENT CHECKPOINT INHIBITION

The first immune checkpoint inhibitor to establish a role in the treatment of mRCC was nivolumab, an anti-PD-1 monoclonal antibody. In the Phase III CheckMate-025 trial, patients with mRCC who had been treated with up to 2 prior anti-angiogenic therapies were randomized to receive either nivolumab or everolimus, an inhibitor of mammalian target of rapamycin (mTOR), approved for use in patients with refractory mRCC [13]. The study was powered for superiority and met its primary endpoint of overall survival (OS), with a median OS of 25 months with nivolumab versus 19.6 months with everolimus (HR: 0.73, 98% CI: 0.57–0.93; p=0.002). The ORR of nivolumab was 25% in this study. The incidence of Grade 3 or higher adverse events (AEs) was 19% in the nivolumab arm compared to 37% in the everolimus arm. On the strength of these findings, nivolumab was approved by the Food and Drug Administration (FDA) for the treatment of mRCC progressed after anti-angiogenic therapy in 2015.

More recently, immune checkpoint inhibition has been studied in treatment-naïve patients with advanced RCC in the Phase II KEYNOTE-427 study [14]. This single-arm, open-label study enrolled patients with ccRCC (cohort A) and those with nccRCC (cohort B) who were

treated with pembrolizumab, an anti-PD-1 monoclonal antibody. Interim results from the ccRCC cohort of 110 patients were reported, with a finding of an ORR of 38.2%, and CR rate of 2.7%. Data for OS are not yet mature, and at the time of analysis, the duration of response endpoint was not yet reached. Treatment-related AEs ≥ Grade 3 were reported in 22.7% of patients. A summary of single agent checkpoint inhibitor therapy is shown in Table 1.

DUAL CHECKPOINT INHIBITION

Based on data demonstrating improved efficacy when nivolumab was combined with ipilimumab, an anti-CTLA4 antibody in patients with metastatic melanoma, immune checkpoint inhibitor combination had potential for efficacy in mRCC [15]. After demonstrating promising results in earlier phase studies, the Phase III CheckMate-214 trial was conducted, randomizing patients with treatment-naïve mRCC to receive either nivolumab plus ipilimumab or sunitinib, a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF TKI), approved for first-line treatment of mRCC [16, 17]. Patients randomized to the nivolumab plus ipilimumab arm received the combination every 3 weeks for 4 cycles, after which they continued to receive nivolumab every 2 weeks. Patients randomized to receive sunitinib were treated once daily for 4 weeks out of a 6-week cycle. Patients were stratified by good-, intermediate-, or poor-risk, defined by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria; the study was designed to evaluate primary endpoints of OS, ORR, and progression-free survival (PFS).

This large study of 1096 patients found that the combination of nivolumab plus ipilimumab resulted in a greater median OS as compared to sunitinib in intermediate- and poor-risk patients (HR: 0.63; $p<0.001$) [17]. The ORR was 42% in the combination as compared to 27% in the sunitinib alone arm; 9% CR rate was observed with dual immune checkpoint inhibition as compared to 1% with sunitinib alone. In good-risk patients, no significant difference was seen between the combination of nivolumab plus ipilimumab as compared to sunitinib. Treatment-related AEs were high in both groups, with 93% in the combination group and 97% in the sunitinib group. Grade 3–4 AEs occurred in 46% of patients in the combination group, compared to 63% in the sunitinib group. Notably, of the patients who had treatment-related AEs in the nivolumab plus ipilimumab arm, 35% of those patients required high dose glucocorticoid treatment to address this.

Based on these results, the FDA approved the combination of nivolumab plus ipilimumab for the treatment of treatment-naïve patients with mRCC who are considered intermediate- or poor-risk by IMDC criteria. This new standard of care was met with some concern because of the concern for immune-related AEs with the combination of nivolumab plus ipilimumab. Thus, other combinations were also studied, which are further discussed. A summary of efficacy of combination therapy is demonstrated in Table 2.

CHECKPOINT INHIBITOR COMBINATIONS WITH ANTI-ANGIOGENIC THERAPY

Therapies targeting VEGF have been an integral component of treatment of mRCC for over a decade. Bevacizumab, an antibody that binds VEGF, was approved in combination with interferon-α for the treatment of mRCC, and exhibited modulatory effects on the immune environment [18]. This suggested possible benefit to combining bevacizumab with atezolizumab, an anti-PD-L1 monoclonal antibody. On the basis of promising early clinical studies, a Phase III, open-label study (IMmotion151) evaluated untreated patients with mRCC; patients were randomized to receive atezolizumab plus bevacizumab every 3 weeks or sunitinib daily for 4 weeks out of 6 weeks [19, 20]. Patients were stratified on the basis of PD-L1 expression, presence of liver metastases, and by prognostic risk as defined by Memorial Sloan Kettering Cancer Center (MSKCC) scoring. The co-primary endpoints of the study were PFS in patients with PD-L1 positive disease and OS in the intention-to-treat (ITT) population. Of the 915 patients enrolled on the trial, 362 (40%) had positive PD-L1 expression. In the PD-L1 positive groups, PFS was longer with the combination of atezolizumab plus bevacizumab compared to sunitinib (11.2 versus 7.7 months, HR= 0.74, 95% CI: 0.57–0.96; p=0.0217) [20]. The ORR among PD-L1 positive patients was 43% for the combination group versus 35% in the sunitinib group. For the co-primary endpoint of OS in the ITT population, statistical significance was not met between the two groups. Treatment-related Grade 3 and higher AEs were observed in 40% of patients receiving atezolizumab plus bevacizumab versus 54% of patients receiving sunitinib. Overall, the study met one but not both co-primary endpoints, and as of this review, the combination has not been approved for first-line use in mRCC.

Clinical studies have also combined immune checkpoint inhibitors with VEGF tyrosine kinase inhibitors (TKIs). A Phase I/II study combining pembrolizumab with pazopanib, a VEGF TKI which was approved for treatment-naïve mRCC, was found to cause considerable dose-limiting hepatotoxicity when pembrolizumab was administered concurrently with pazopanib [21]. Within the study, another treatment regimen was evaluated, utilizing a pazopanib run-in prior to combining with pembrolizumab; while hepatotoxicity was not dose-limiting in that cohort of patients, there were considerable AEs including increased amylase, lipase, diarrhea, confusion, nausea, pulmonary embolism, and pneumonitis. Another Phase I trial, CheckMate 016, enrolled two cohorts of mRCC patients to treatment with nivolumab plus sunitinib or pazopanib [22]. Both combinations were accompanied by significant dose-limiting toxicities (DLTs); in fact, the combination of nivolumab plus pazopanib was closed to expansion due to DLTs. While the combination of nivolumab plus sunitinib did proceed to expansion, all patients had treatment-related AEs and 82% were Grade 3 or higher; 39% of patients discontinued treatment due to treatment-related AEs.

While sunitinib and pazopanib were thus considered too toxic to explore in combination with checkpoint inhibition, a more recently developed VEGF TKI, axitinib, had exhibited a lower incidence of hepatotoxicity as a single agent [23, 24]. A Phase Ib study evaluated the combination of axitinib with avelumab, an anti-PD-L1 monoclonal antibody, with only one

DLT observed [25]. While there was still a significant rate of Grade or higher treatment-related AEs (58%), the combination was further studied. The Phase III study, JAVELIN Renal 1010, randomized patients with untreated mRCC to receive either avelumab plus axitinib or sunitinib [26]. The co-primary endpoints of the study were PFS and OS among patients with PD-L1 positive tumors. Of the 886 patients enrolled to the trial, 560 (63.2%) had PD-L1 positive tumors. In that patient population, PFS was 13.8 months with the combination versus 7.2 months with sunitinib (HR: 0.61, 95% CI: 0.47–0.79; $p<0.001$). There was not a significant difference in OS among these patients, though median follow-up for the study was 11.6 months for the combination, and 10.7 months for sunitinib, indicating that data may not yet be mature. There was a higher ORR of 55.2% with avelumab plus axitinib versus 25.5% with sunitinib. Across the complete study population, median PFS was longer with avelumab plus axitinib versus sunitib (13.8 months versus 8.4 months, HR: 0.69, 95% CI: 0.56–0.84; $p<0.001$). Grade 3 or higher treatment-related AEs were observed in 71.2% of patients receiving avelumab plus axitinib versus 71.5% of patients receiving sunitinib. Discontinuation of avelumab plus axitinib occurred in 7.6% of patients while 13.4% of patients receiving sunitinib discontinued treatment due to AEs. The FDA has approved this combination for the first-line treatment of patients with mRCC.

Axitinib has also been studied in combination with pembrolizumab, first in a Phase Ib study, in which 65% of patients had Grade 3 or higher treatment-related AEs [27]. The Phase III KEYNOTE-426 trial then randomized treatment-naïve mRCC patients to receive either pembrolizumab plus axitinib or sunitinib [28]. The co-primary endpoints for this study were OS and PFS in the ITT population. The study met both of its endpoints, with median PFS of 15.1 months in the pembrolizumab plus axitinib group versus 11.1 months in the sunitinib group (HR: 0.69, 95% CI: 0.57–0.84; $p<0.001$). The percentage of patients alive at 12 months was 89.9% in the pembrolizumab plus axitinib group versus 78.3% in the sunitinib group. Median OS was not reached in either group, but the risk of death was 47% lower in the pembrolizumab plus axitinib group, with HR: 0.53, 95% CI: 0.38–0.74; $p<0.0001$). There was also a higher ORR of 59.3% in the pembrolizumab plus axitinib group compared to 35.7% in the sunitinib group, which was statistically significant. The combination of pembrolizumab plus axitinib has also been approved by the FDA for the first-line treatment of mRCC.

A phase I study evaluated cabozantinib, a multikinase inhibitor, in combination with immune checkpoint inhibitors in genitourinary malignancies [29]. The study enrolled small numbers of patients with mRCC, with 7 receiving the combination of nivolumab and cabozantinib, and 6 receiving the combination of nivolumab plus ipilimumab plus cabozantinib. Data from that trial of a total of 75 patients showed treatment-related AEs ≥ Grade 3 in 62% of patients receiving cabozantinib plus nivolumab, and in 71% of patients receiving cabozantinib plus nivolumab plus ipilimumab. A Phase III trial, CheckMate 9ER (NCT03141177), randomizes patients to receive either nivolumab combined with cabozantinib or sunitinib in treatment-naïve mRCC patients; results may be available in the next 1–2 years. In addition, a Phase III trial (COSMIC-313, NCT03937219) has just been initiated, evaluating the combination of cabozantinib with nivolumab and ipilimumab versus nivolumab and ipilimumab in patients with IMDC-defined intermediate and poor-risk

mRCC. These studies will provide information as to whether there is clinical benefit to combining cabozantinib to immune checkpoint inhibitors.

IMMUNE CHECKPOINT INHIBITORS IN NON-CLEAR CELL RENAL CELL CARCINOMA

While clear cell RCC is the most common subtype of RCC, the World Health Organization (WHO) recognize 15 additional distinct histologic subtypes of RCC, often referred to as non-clear cell (ncc) RCC [30]. While many of these histologic subtypes have been found to have distinct associated genetic mutations and distinct prognoses, nccRCC subtypes tend to be studied as a group because of their low incidence in comparison to clear cell subtype. As the role of immune checkpoint inhibitors are now established for clear cell RCC, studies have been initiated to evaluate the efficacy of these therapies in nccRCC with some preliminary data available to date.

The KEYNOTE-427 study evaluating pembrolizumab monotherapy included a cohort of 165 patients with previously untreated nccRCC. Of the subtypes, patients either had papillary RCC (n=118, 71%) or chromophobe RCC (n=21, 13%); the remainder had unclassified subtype (n=26, 16%). In the overall cohort of nccRCC patients, the ORR was 24.8%; patients with papillary RCC exhibited ORR of 25.4%, while chromophobe RCC patients had ORR of 9.5% and unclassified subtype patients had ORR of 34.6% [31].

The CheckMate-374 study established efficacy of a flat dose of nivolumab, but also included a separate cohort of nccRCC patients [32]. Patients could have previously been treated with 1–2 prior systemic anti-VEGF therapies, but most patients were treatment-naïve (n=29, 66%). While ORR was an exploratory endpoint for this trial, of the 44 patients in the nccRCC cohort, an ORR of 13.6% was observed. Again, patients primarily had papillary subtype (n=24), with chromophobe (n=7) and unclassified (n=8) as well as other (n=5) represented in the cohort. Responses were seen among patients who had chromophobe, papillary, collecting duct, and unclassified RCC, indicating that anti-PD-1 therapy could have activity across histologic subtypes.

A Phase II study evaluated atezolizumab and bevacizumab in patients with nccRCC as well as patients with clear cell RCC with >20% sarcomatoid differentiation [33]. It is important to note that while RCC with sarcomatoid differentiation is considered clear cell RCC, the disease behaves differently, has a more aggressive phenotype, and a poor prognosis [34]. In this single-arm, open-label study, patients could have received any number of prior therapies. Of those evaluated for response, 36 patients had nccRCC (papillary n=14, chromophobe n=8, unclassified n=3, collecting duct n=3, translocation n=3, and other n=5) and 16 had clear cell RCC with sarcomatoid differentiation. Across the entire cohort, the ORR was 31%; across the nccRCC cohort, ORR was 25%, while patients with clear cell RCC with sarcomatoid differentiation were found to have ORR of 44% [33].

These data support retrospective studies that have evaluated the use of PD-1 and PD-L1 inhibitors in patients with nccRCC or patients with sarcomatoid differentiation, which similarly show that checkpoint inhibitors have efficacy in these disease subtypes [35]. Based

on current data, the use of immune checkpoint inhibitors, in combination with anti-VEGF agents or alone, is certainly an option for patients with nccRCC.

IMMUNE-RELATED ADVERSE EVENTS

Immune checkpoint inhibitors can cause a variety of immune-related adverse events (IRAEs), some of which will be encountered not infrequently by the practicing nephrologist who should thus be keenly aware of them. The exact mechanism for these has not been fully elucidated, but there are hypotheses on contributors to the pathophysiology. For example, it is known that CTLA4 and PD-1/PD-L1 in normal hosts maintain T-cell homeostasis that allows for self-tolerance; when self-tolerance is not maintained, autoimmune diseases can develop [36, 37]. Immune checkpoint inhibition may also lead to autoreactive T-cells due to a shared antigen between tumor and normal tissue, such as has been seen in the development of myositis [38]. Anti-PD-1 and anti-PD-L1 therapy may also play a role in humoral immunity, which could enhance preexisting autoantibodies, such as can be observed with the development of hypothyroidism [39]. Cytokines are also hypothesized to be involved in IRAEs. For example, patients with ipilimumab-induced colitis were found to have elevated levels of interleukin-17 (IL-17) [40].

Though IRAEs tend to manifest early in treatment course, they can occur at any point while on immune checkpoint inhibitor therapy, and in fact even after treatment has been discontinued [41]. Thus, regular clinical assessment of patients on these therapies is critical. In addition, given the extent and severity of IRAEs that can occur with these therapies, patients with preexisting autoimmune conditions, especially those requiring active therapy, were excluded from the seminal trials evaluating the efficacy and safety of immune checkpoint inhibitors. So, generally it is recommended that other therapies be considered for these patients.

Immune checkpoint inhibition can lead to IRAEs in any organ, but some IRAEs are common, and others are of note due to their severity or irreversibility. Fatigue, pruritus and rash are some of the most common adverse events seen with immune checkpoint inhibitors, but do not commonly lead to treatment discontinuation. More concerning, but less common IRAEs, such as adrenal insufficiency, autoimmune hepatitis, adrenal insufficiency, colitis, Type 1 diabetes mellitus, hypophysitis, myocarditis, Myasthenia Gravis, nephritis or pneumonitis require clinician vigilance, because of the dire consequences of delaying management of these IRAEs.

In the clinical studies that evaluated immune checkpoint inhibitors and their combinations, there were both similarities and nuances in the adverse events seen with these treatments. All of the studies had a high rate of all Grade AEs, as outlined in Table 3. Though rare, deaths were observed from treatment-related AEs in these studies. In the KEYNOTE-426 trial of pembrolizumab plus axitinib, treatment-related deaths were seen in 11 patients, with causes including myasthenia gravis, myocarditis, cardiac arrest, pneumonitis, and pulmonary embolism [28]. With the combination of avelumab and axitinib, 3 treatment-related deaths were reported due to myocarditis, sudden cardiac death and necrotizing pancreatitis [26]. These observations underscore the severity of treatment-related AEs in mRCC, and the

importance of early intervention. As outlined in Table 3, a significant portion of patients receiving nivolumab plus ipilimumab (22%) and pembrolizumab plus axitinib (30.5%) had to discontinue at least one of their treatments due to AEs. Similarly, a significant portion of patients required treatment with glucocorticoids across studies, though at varying rates; the KEYNOTE-426 did not report the rate of patients requiring glucocorticoid treatment.

Table 4 outlines some of the common adverse effects of interest seen in these treatments. While fatigue is a common adverse effect of immune checkpoint inhibitors, Grade 3 or higher fatigue rates are low across treatments. Similarly rash and pruritus are commonly seen with immune checkpoint inhibitors, but very low rates of Grade 3 or higher rash was observed across trials. Palmar-plantar erysthodysesthesia (PPE) has been seen in combination trials, which is somewhat expected as PPE is a common AE seen with VEGF-directed therapies. Thus, it is also unsurprising that PPE was not seen in patients treated with monotherapy.

Though ≥ Grade 3 colitis was reported as rare across trials, diarrhea was reported as a common adverse effect across trials, and these included ≥ Grade 3 AEs. This does pose some difficulty in interpretation, as differentiating clinically between diarrhea and colitis can be challenging. Furthermore, VEGF-directed therapies are known to cause diarrhea, so it can be difficult to assess the cause of symptoms.

Increasing evidence suggests that patients who develop IRAEs may be more likely to respond to immune checkpoint inhibitors in other tumor types [42, 43, 44]. A small study evaluating patients with metastatic RCC who discontinued anti-PD-1 or anti-PD-L1 therapy for IRAEs has been reported [45]. These 19 patients had already experienced a clinical response, then discontinued all systemic therapy after development of IRAE. These patients were mostly treated in the second-line setting. While the median time on therapy was 5.5 months, the median time to progression (TTP) was 18.4 months (95% CI, 4.7–54.3); 13 (68.4%) patients had TTP of at least 6 months or longer. These data indicate that, regardless of whether IRAEs are associated with efficacy, patients who must discontinue therapy due to development of IRAEs may maintain response to therapy and may enjoy a significant treatment-free interval.

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Of utmost importance when treating patients with RCC with immune checkpoint inhibitors is awareness and experience in managing the toxicity associated with these therapies. Depending on the severity and the type of IRAE, management varies, but the American Society of Clinical Oncology (ASCO) created practice guidelines for management of these toxicities [46]. The overarching principles of these guidelines are that patient and caregiver education about IRAEs is important, and that significant IRAEs often require multidisciplinary team management.

Of particular interest to the practicing nephrologist of acute kidney injury (AKI) precipitated by immune checkpoint inhibitor therapy. This is an infrequent adverse event based on the seminal clinical trials evaluating immune checkpoint inhibitor therapy in mRCC.

Nevertheless, AKI has been reported in the literature and is a known adverse effect of therapy, and involvement of nephrologists as early as possible is recommended. When affected patients have been evaluated by biopsy for AKI, acute tubulointerstitial nephritis (AIN) is the dominant pattern of injury [47]. However, acute tubular necrosis (ATN) has also been identified in patients receiving pembrolizumab, though the mechanism for pembrolizumab-induced ATN is not known [48]. Thus, nephrologists should be involved to determine if a biopsy might assist with management. Patients are treated with both hydration and glucocorticoids, and for those patients with AIN, at least partial recovery of kidney function is usually observed. However, patients with ATN do not always have resolution of symptoms.

In general, Grade 1 toxicities do not require treatment interruptions and can often be managed by close monitoring alone. Most Grade 2 toxicities do require temporary suspension of checkpoint inhibitor therapy. Exceptions for which holding checkpoint inhibitor therapy is optional and at the discretion of the practitioner are inflammatory dermatitis or rash, pruritus, or thyroid dysfunction. Depending on associated symptoms, initiation of corticosteroids (at a 0.5 to 1 mg/kg/day prednisone equivalent dosing) is indicated, with a subsequent taper once the AE resolves. For some Grade 2 toxicities, such as myositis, nephritis, neurologic or ocular toxicities, consultation with a subspecialist is recommended as early in detection of symptoms as possible.

Certainly, if Grade 3 AEs develop, subspecialty consultation is necessary. For example, a gastroenterologist should be consulted for Grade 3 colitis, an endocrinologist should be consulted for Grade 3 hypophysitis. Initiation of corticosteroids (at a 0.5 to 1 mg/kg/day prednisone equivalent dosing) is indicated for Grade 3 toxicities, with a slow taper once the AE resolves. For Grade 3 toxicities, infliximab, a chimeric monoclonal antibody which binds to TNF α, is recommended if a patient is not showing some improvement in AE within 48–72 hours of initiation of corticosteroids. Infliximab is not recommended to be given in cases of autoimmune hepatitis, because of a known reported risk of development of transaminitis with infliximab such that there is a theoretical risk of liver failure though this has not been reported to have happened to date.

Most cases of Grade 4 IRAEs require permanent discontinuation of immune checkpoint inhibitor therapy. The exception is the development of Grade 4 endocrinopathies, that have been adequately controlled by hormone replacement.

Specific to the management of patients with RCC, the toxicities associated with combination therapy of an immune checkpoint inhibitor and antiangiogenic agent can present unique challenges, which need to be considered. Palmar-plantar erythrodysesthesia has been reported with axitinib as well as bevacizumab monotherapies and must be distinguished from immune-related rashes of the hand, as it sometimes requires dose reduction or suspension of the anti-angiogenic agent [49, 50]. Axitinib as monotherapy also can cause hypothyroidism, diarrhea, transaminitis, cough and dyspnea [50]. Thus, with the combinations of pembrolizumab and axitinib or avelumab and axitinib, careful consideration must be taken in assessing an adverse effect to determine if it is immune-related or induced

by axitinib. A low index of suspicion must be kept for immune-related AEs, as these can intensify in severity if not adequately managed upon first presentation.

PREDICTING RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

To date, there are not definitive biomarkers that are routinely employed in patient selection for the treatment of advanced RCC. The most developed marker remains PD-L1 status as assessed by immunohistochemical (IHC) staining, but there is discordance in findings as well as how this marker is used across studies. In a Phase II trial (IMMmotion150) comparing atezolizumab plus bevacizumab versus atezolizumab alone versus sunitinib alone, PD-L1 was defined to be positive if ≥ 1% [19]. Patients with PD-L1 positive status in this study had a trend towards improved PFS when treated atezolizumab plus bevacizumab or atezolizumab as compared to sunitinib, though it was not statistically significant. In the subsequent IMmotion 151 Phase III study, patients with PD-L1 positive disease by the definition aforementioned had a significantly higher PFS when treated with atezolizumab plus bevacizumab versus sunitinib [20].

The CheckMate-025 Phase III trial comparing nivolumab to everolimus stratified PD-L1 expression by IHC by ≥ 1% versus <1%, or as ≥ 5% versus <5%. With either of these definitions of PD-L1 status, PD-L1 expression did not predict response to nivolumab [13]. The CheckMate-214 Phase III trial evaluating the combination of nivolumab plus ipilimumab versus sunitinib evaluated patients as PD-L1 positive if IHC expression was ≥ 1% [15]. In that study, PD-L1 expression > 1% correlated to longer OS with immune checkpoint therapy.

The KEYNOTE-427 study evaluating pembrolizumab monotherapy did evaluate patients with PD-L1 IHC expression ≥ 1% versus those with < 1% [14]. Those with PD-L1 expression ≥ 1% demonstrated a higher ORR (50%) compared to those with negative PD-L1 expression (26%). The KEYNOTE-426 Phase III study evaluating the combination of pembrolizumab plus axitinib versus sunitinib similarly evaluated patients with positive PD-L1 expression by this definition. Pembrolizumab plus axitinib exhibited better OS and PFS regardless of PD-L1 expression.

The JAVELIN Renal 101 Phase III trial comparing avelumab plus axitinib versus sunitinib also defined PD-L1 positivity as ≥ 1% by IHC [26]. In fact, the primary endpoints of the study of OS and PFS were specific to PD-L1 positive tumors. Among PD-L1 positive patients, avelumab plus axitinib was superior to sunitinib in terms of PFS; OS was not significantly different but may be secondary to short follow-up. However, as a secondary endpoint of the trial, PFS irrespective of PD-L1 status was significantly longer with avelumab plus axitinib; OS, again, was not significantly different.

These data, in sum, indicate that PD-L1 status is somewhat associated with response to immune checkpoint inhibitors, but responses are seen in patients whose tumors do not exhibit PD-L1 expression. Thus, PD-L1 status is insufficient to clearly exclude patients from treatment with immune checkpoint therapy.

CONCLUSIONS:

Over a short course of time, immune checkpoint inhibitors have become an important component of treatment of patients with advanced or metastatic renal cell carcinoma. Increasingly, the combination of an immune checkpoint inhibitor with an anti-angiogenesis agent appears to have broad application across patients with newly diagnosed metastatic disease, regardless of IMDC risk classification. Outcomes have undoubtedly improved for patients with metastatic RCC as a result of these therapies. The toxicity profile of immune checkpoint inhibitors does require frequent clinical assessment, and practitioner education on early intervention with immunosuppressive therapies and on involvement of subspecialists. There are real challenges associated with identification of the relationship between toxicity and immune checkpoint inhibitor or anti-angiogenesis agent when treating with the combination of the two. Finally, to date, there are not good established biomarkers for identifying patients who are less likely to respond to these therapies; this is an important future area of research given the financial toxicity as well as the IRAEs associated with these drugs.

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49. Bevacizumab FDA package insert

50. Axitinib FDA package insert

Table 1:

Summary of Efficacy of Single Agent Checkpoint Inhibitors

Trial/Monotherapy	Prior Treatment	N	ORR (95% CI)	PFS months (95% CI)	OS months (95% CI)
CheckMate-025 Nivolumab[13]	1–2 anti-angiogenesis agents	821	25%	4.6 (3.7–5.4)	25.0 (21.8− not estimable)
KEYNOTE-427 Cohort A Pembrolizumab[14]	Therapy-naïve	110	36.4% (27.4–46.1)	7.1 (5.6–11.0)	Not reached
IMmotion150 Atezolizumab[19]	Therapy-naive	103	25% (17–35)	6.1 (5.4–13.6)	Not reported

Table 2:

Summary of Efficacy in First-Line Checkpoint Inhibitor Combination Trials

Trial/ Combination	Population (for primary endpoints)	OS months	OS rate (95% CI)	PFS months (95% CI)	ORR (95% CI)	CR	Median time to response months (95% CI)	Median duration of response months (95% CI)
CheckMate 214 (nivolumab + ipilimumab)[17]	IMDC Intermediate & poor-risk	Not reached	75% (70–78) at 18 months	11.6 (8.7–15.5)	42% (37–47)	9%	2.8 (0.9–11.3)	Not reached (21.8-not estimable)
KEYNOTE 426 (pembrolizumab + axitinib)[27]	Unselected	Not reached	82.3% (77.2–86.3) at 18 months	15.1 (12.6–17.7)	59.3% (54.5–63.9)	5.8%	2.8 (1.5–16.6)	Not reached (>1.4 – >18.2)
JAVELIN Renal 101 (avelumab + axitinib)[26]	PD-L1 positive patients	(insufficient follow-up)	(insufficient follow-up)	13.8 (11.1-not estimable)	55.2% (49.0–61.2)	4.4%	1.6 (1.2–10.1)	Not reached
IMMotion 151 (atezolizumab + bevacizumab)[20]	PD-L1 positive patients Overall population	(insufficient follow-up)	(insufficient follow-up)	11.2 11.2	43% (35–50) 37% (32–41)	9% 5%	Not reported	NR (12-NR) 16.6 (15-NR)

Table 3:

Overall Rate (%) of Adverse Events and Treatment Modifications with Immune Checkpoint Inhibitors

	Nivolumab[13]	**Pembrolizumab**[14]	**Nivolumab + ipilimumab**[17]	**Pembrolizumab + axitinib**[28]	**Avelumb + Axitinib**[26]	**Atezolizumab + bevacizumab**[20]
Trial	CheckMate-025	KEYNOTE-427	CheckMate-214	KEYNOTE-426	JAVELIN RENAL 101	IMmotion-151
All Grade AEs	78.5%	80%	97.4%	98.4%	99.5%	91.3%
> Grade 3 AEs	19%	21.8%	46.7%	75.8%	71.2%	40.3%
Deaths	--	0.9%	1.8%	2.6%	0.7%	1.1%
% treatment discontinued due to AEs	8%	10.9%	22%	30.5%	7.6%	1.9%
% treated with high-dose glucorticoids for AEs	Not reported	12.7%	27.7%	Not reported	11.1%	16.6%

Table 4:

Rate of Select Adverse Events (%) in Key mRCC Immune Checkpoint Inhibitor Trials

	Nivolumab[13]	**Pembrolizumab[14]**	**Nivolumab + ipilimumab[17]**	**Pembrolizumab + axitinib[28]**	**Avelumab + axitinib[26]**	**Atezolizumab + bevacizumab[20]**
Trial	CheckMate-025	KEYNOTE-427	CheckMate-214	KEYNOTE-426	JAVELIN RENAL 101	IMmotion-151
Fatigue	2.5%	--	4%	2.8%	3.5%	4.3%
Rash	<1%	1.8%	1%	0.2%	0.5%	Not reported
Palmar-plantar erysthodysesthesia	--	--	--	5.1%	5.8%	--
Hypertension	--	--	<1%	22.1%	25.6%	13.9%
Proteinuria	--	--	--	2.8%	--	<3%
Diarrhea	1.2%	3.6%	4%	9.1%	6.7%	22%
Transaminitis	--	1.8%	--	See below	See below	Not reported
AST elevation	--	Not reported	--	13.3%	6%	Not reported
ALT elevation	--	Not reported	--	7%	3.9%	Not reported
Colitis	--	2.7%	--	--	--	--
Anemia	1.8%	--	<1%	0.7%	1.6%	--
Thyroid dysfunction	--	--	<1%	0.2	0.2	Not reported
Pneumonitis	1.5%	0.9%	--	0.2%	--	--