Immune checkpoint inhibitors in advanced renal cell carcinoma: experience to date and future directions

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In recent years, there has been dramatic expansion of the treatment armamentarium for patients with advanced renal cell carcinoma (aRCC), including drugs targeting vascular endothelial growth factor and mammalian target of rapamycin (mTOR) pathways. Despite these advances, patient outcomes remain suboptimal, underscoring the need for therapeutic interventions with novel mechanisms of action. The advent of immunotherapy with checkpoint inhibitors has led to significant changes in the treatment landscape for several solid malignancies. Specifically, drugs targeting the programmed death 1 (PD-1) and cytotoxic T-lymphocyte associated antigen (CTLA-4) pathways have demonstrated considerable clinical efficacy and gained regulatory approval as single-agent or combination therapy for the treatment of patients with metastatic melanoma, non-small cell lung cancer, aRCC, advanced squamous cell carcinoma of the head and neck, urothelial cancer and Hodgkin lymphoma. In aRCC, the PD-1 inhibitor nivolumab was approved in both the United States and Europe for the treatment of patients who have received prior therapy, based on improved overall survival compared with the mTOR inhibitor everolimus. Other checkpoint inhibitors, including the CTLA-4 inhibitor ipilimumab in combination with several agents, and the PD-L1 inhibitor atezolizumab, are in various stages of clinical development in patients with aRCC. In this review, current evidence related to the clinical use of checkpoint inhibitors for the treatment of patients with aRCC is discussed, including information on the frequency and management of unconventional responses and the management of immune-related adverse events. In addition, perspectives on the future use of checkpoint inhibitors are discussed, including the potential value of treatment beyond progression, the potential use in earlier lines of care or in combination with other agents, and the identification of biomarkers to guide patient selection and enable individualization of therapy.

Key words: immune checkpoint inhibitors, renal cell carcinoma, anti-PD-1/PD-L1, anti-CTLA-4, overall survival

Introduction to renal cell carcinoma and approved treatments

Worldwide, an estimated 338,000 cases of renal cell carcinoma (RCC) are diagnosed annually, with 144,000 attributed deaths [1]. The annual incidence of kidney cancer is ~63,000 in the United States [2]. Approximately 30% of patients will be diagnosed with locally advanced or metastatic disease RCC and as many as 40% develop metastasis after primary surgical treatment of localized RCC [3]. Prognosis for patients with advanced RCC (aRCC) has dramatically improved over the past decade; however, the vast majority of patients will ultimately die of their disease. Therefore, additional treatment options are needed.

Clear-cell RCC comprises 80%–90% of all RCC cases. Increased angiogenesis is the hallmark of clear-cell RCC, and enhanced vascular endothelial growth factor (VEGF)/VEGFR receptor (VEGFR) signaling—and to a lesser extent, mammalian target of rapamycin (mTOR) activity—are important factors underlying dysregulated angiogenesis in RCC [4].

Treatment of aRCC has improved significantly with the introduction and regulatory approval of agents that block VEGF or mTOR pathways and significantly improve objective response rate (ORR) and/or median progression-free survival (PFS) compared with previous treatment approaches [5, 6] (Table 1).

Since 2005, the US Food and Drug Administration (FDA) has approved VEGFR tyrosine kinase inhibitors (TKIs) sorafenib,
sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib, the anti-VEGF antibody bevacizumab (in combination with interferon) and mTOR inhibitors everolimus and temsirolimus for treatment of patients with aRCC. Cabozantinib is a multikinase inhibitor targeting VEGFR, MET and AXL; approved by the FDA in April 2016 for patients with aRCC who have received prior anti-VEGF therapy [7, 8]. Lenvatinib, a multireceptor TKI (which inhibits both VEGFR and the fibroblast growth factor receptor), in combination with everolimus was also approved by the FDA (May 2016) as therapy for aRCC following 1 prior antiangiogenic therapy [7, 8].

Table 1. Second-line therapy options (other than a clinical trial) for aRCC (relapsed, stage IV and surgically unresectable disease with predominantly clear-cell histology)—National Comprehensive Cancer Network (NCCN) and ESMO guidelines [5, 6]

<table>
<thead>
<tr>
<th>NCCN* (alphabetical by category and preference)</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (category 1, preferred)b</td>
<td>After antiangiogenic therapy</td>
</tr>
<tr>
<td>Nivolumab (category 1, preferred)b</td>
<td>Nivolumab [I, A]</td>
</tr>
<tr>
<td>Axitinib (category 1)</td>
<td>Cabozantinib [I, A]</td>
</tr>
<tr>
<td>Lenvatinib + everolimus (category 1)</td>
<td>Axitinib [II, B]</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Everolimus [II, B]</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Sorafenib [III, B]</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>After cytokine therapy</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Axitinib [I, A]</td>
</tr>
<tr>
<td>Bevacizumab (category 2B)</td>
<td>Sorafenib [I, A]</td>
</tr>
<tr>
<td>HD IL-2 for selected patientsc (category 2B)</td>
<td>Pazopanib [II, A]</td>
</tr>
<tr>
<td>Temsirolimus (category 2B)</td>
<td>Sunitinib [II, A]</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>May include palliative RT, metastasectomy, bisphosphonates,</td>
</tr>
<tr>
<td></td>
<td>RANK ligand inhibitors for bony metastases</td>
</tr>
</tbody>
</table>

Category 1 (NCCN): based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2A (NCCN): based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. All recommendations are category 2A unless otherwise noted; Category 2B (NCCN): based on lower-level evidence, there is NCCN consensus that the intervention is appropriate; Level of evidence I (ESMO): evidence from at least one large randomized, controlled trial of good methodological quality or meta-analyses of well conducted randomized trials without heterogeneity; Level of evidence II (ESMO): small randomized trials or large randomized trials with a suspicion of bias or meta-analyses of such trials or of trials with demonstrated heterogeneity; Level of evidence III (ESMO): prospective cohort studies; Grade of recommendation A: strongly recommended by ESMO committee; Grade of recommendation B: generally recommended by ESMO committee.

Categories and Grades:
- Category 1 (NCCN): based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2A (NCCN): based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2B (NCCN): based on lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- Level of evidence I (ESMO): evidence from at least one large randomized, controlled trial of good methodological quality or meta-analyses of well conducted randomized trials without heterogeneity.
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- Level of evidence III (ESMO): prospective cohort studies.
- Grade of recommendation A: strongly recommended by ESMO committee.
- Grade of recommendation B: generally recommended by ESMO committee.

May include palliative surgery or RT, metastasectomy, bisphosphonates, RANK ligand inhibitors for bony metastases.

CheckMate 025 study of nivolumab versus everolimus in patients who had received prior antiangiogenic therapy for aRCC [14].

**Background on ICI therapy**

The immune system is typically able to recognize cancer cells through recognition of mutated proteins, known as neoantigens, expressed on the surface of tumor cells to mount antitumor responses. T cells require multiple signals to become fully activated, and T-cell checkpoint pathways reduce inappropriate or sustained immune activation, including immune responses to self-antigens. Tumors may exploit immune checkpoint pathways to escape an immune attack. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) are examples of co-inhibitory checkpoint molecules [15].

CTLA-4, the first immune checkpoint receptor to be clinically targeted, is expressed exclusively on T cells. It considered to regulate early stages of T-cell activation (T-cell priming), primarily by
counteracting activity of the T-cell co-stimulatory receptor CD28, thereby shutting off early T-cell responses [15].

In contrast to CTLA-4, the major role of PD-1 is limiting activity of T cells in peripheral tissues during an immune response to foreign antigens including those expressed by infectious agents [15, 16] (Figure 1). PD-1 checkpoint inhibitors selectively block interactions between PD-1, expressed on activated T cells, and PD-1 ligands 1 and 2 (PD-L1 and PD-L2), which are expressed on immune cells and tumor cells [17]. Interaction between PD-1 and its ligands normally results in inhibition of cellular immune responses. In many tumors, PD-L1 expression identifies tumors recognized by the immune system, which consequently appear to have a better prognosis. In contrast, RCC tumors with increased PD-L1 expression, for reasons yet to be determined, have worse prognoses [18, 19]. Disruption of PD-1/PD-L1-mediated signaling through PD-1 inhibitors may restore immune response and effective antitumor immunity [20].

ICIs in development or approved for use in advanced cancer

Several immune checkpoint antibodies targeting CTLA-4, PD-1 or PD-L1 are currently approved for use by the FDA (ipilimumab, nivolumab, pembrolizumab, atezolizumab) and/or undergoing phase III clinical investigation for treatment of several types of cancer (Table 2) [17, 21].

Treatment with ICIs has been associated with improved response rates in many malignancies, and overall survival (OS) in melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer, and aRCC. Phase II and III investigations in several other malignancies (Merkel cell, triple-negative breast, gastric, hepatocellular, among others) are currently underway [17, 21].

Ipilimumab was the first ICI approved by the FDA and European Commission; it is approved for treatment of patients with unresectable or metastatic melanoma as monotherapy based on evidence of improved OS in two phase III studies [22, 23], and in combination with nivolumab [24]. Nivolumab monotherapy is approved by the FDA for treatment of patients with BRAF V600 wild-type or mutation-positive, unresectable or metastatic melanoma; metastatic NSCLC who progressed on or after platinum-based chemotherapy; aRCC who have received prior antiangiogenic therapy; and classical Hodgkin lymphoma who had relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin [24]. Nivolumab is approved in Europe as monotherapy for patients with advanced (unresectable or metastatic) melanoma, locally advanced or metastatic NSCLC after prior chemotherapy and aRCC after prior therapy; and recently in combination with ipilimumab for patients with advanced melanoma [13]. Pembrolizumab is approved in the United States and the European Union for treatment of patients with unresectable or metastatic melanoma, including first-line treatment, based on evidence of superior OS versus ipilimumab in a phase III study [25, 26]. Pembrolizumab is also approved for treatment of locally advanced or metastatic NSCLC in patients with progression on or after platinum-based chemotherapy, and for treatment of recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy [13, 24, 26]. Atezolizumab is indicated in the United States for treatment of patients with locally advanced or metastatic urothelial carcinoma who progressed during or after platinum-containing chemotherapy, or within 12 months of
neoadjuvant or adjuvant treatment with platinum-containing chemotherapy [27, 28]. It is also approved for treatment of patients with metastatic NSCLC who progressed during or after platinum-containing chemotherapy [27].

### Clinical development of ICIs in aRCC

#### Ipilimumab

In a phase II study (NCT00057889), CTLA-4 blockade with ipilimumab (3 mg/kg every 3 weeks) induced cancer regression in some patients with metastatic RCC. In a cohort of 40 patients, 26 of whom had received previous IL-2 therapy, five had partial responses (PR) of 7, 8, 12, 17 and 21 months’ duration for an ORR of 12.5% [29].

#### Atezolizumab

In a phase I study (NCT01375842) of PD-L1 blockade with atezolizumab, 70 patients with metastatic RCC, including clear-cell RCC (n = 63) and non-clear-cell RCC (n = 7), received atezolizumab every 3 weeks. Most patients (87%) received prior systemic therapy. The median OS was 28.9 months [95% CI 20.0 months to not reached (NR)] and median PFS was 5.6 months (95% CI 3.9–8.2 months). The ORR was 15% (95% CI 7%–26%) [27].

#### Nivolumab: phase I study data

A phase I study (study 003, NCT00730639) with nivolumab in 296 patients with advanced solid tumors included 34 patients with aRCC. Nivolumab (1 or 10 mg/kg) was administered every 2 weeks. Among patients with aRCC, the ORR was 24% (4 of 17) and 31% (5 of 16) in patients treated with 1.0 and 10.0 mg/kg, respectively [30]. At a minimum of 78 weeks after treatment initiation, the ORR was 29% (10 of 34 patients). Median OS was 22.4 months, with 1-, 2- and 3-year survival rates of 71%, 48% and 44%, respectively. Grade 3/4 treatment-related adverse events (AEs) occurred in 18% of patients; all were reversible [31]. At a minimum follow-up of 50.5 months, the survival rate was 38% at 4 years (Figure 2) [32].

#### Nivolumab clinical development (phase II)

A phase II study (study 010, NCT01354431) assessed antitumor activity, dose-response relationship and safety of nivolumab in patients with aRCC; 168 patients were randomly assigned to 0.3, 2 or 10 mg/kg nivolumab every 3 weeks. Most patients (70%; 118 of 168) received >1 prior systemic treatment regimen. The respective median PFS rates were 2.7, 4.0 and 4.2 months; ORRs were 20%, 22% and 20%. Median OS was 18.2, 25.5 and 24.7 months, respectively. The most common treatment-related AE was fatigue (24%, 22% and 35%, respectively), and 19 patients (11%) experienced grade 3/4 treatment-related AEs [33]. At a minimum follow-up of 49.2 months, the survival rate was 39% at 4 years [32]. Updated analyses found the safety profile to be consistent with prior reports, noting that most select treatment-related AEs occur within the first 6 months of treatment (Figure 2) [32].

#### Nivolumab clinical development (phase III)

Superior OS was subsequently demonstrated by nivolumab versus everolimus in a large international, randomized, open-label

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**Table 2. Immune checkpoint inhibitors currently under investigation/approved for use in advanced tumors**

<table>
<thead>
<tr>
<th>Immune checkpoint inhibitor</th>
<th>Characteristics of monoclonal antibody</th>
<th>Target</th>
<th>Approval status of tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Fully human IgG4</td>
<td>PD-1</td>
<td>FDA approved: melanoma, NSCLC, RCC, Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under investigation: glioblastoma, UC, SCLC, HNSCC, esophageal cancer, MM, HCC, glioblastoma, gastric cancer, SCCA of lung</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Humanized IgG4</td>
<td>PD-1</td>
<td>FDA approved: melanoma, NSCLC, HNSCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under investigation: TNBC, MM, Hodgkin lymphoma, gastric cancer, HCC, UC, esophageal carcinoma, CRC, Merkel cell carcinoma</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Human IgG1</td>
<td>PD-L1</td>
<td>FDA approved: UC, NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under investigation: RCC, TNBC, NSCLC, SCLC, UC, CRC</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Fully human IgG1</td>
<td>PD-L1</td>
<td>FDA approved: UC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under investigation: TNBC, HNSCC, NSCLC, UC, SCCA</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Fully human IgG1</td>
<td>PD-L1</td>
<td>FDA approved for advanced Merkel cell carcinoma treated with prior platinum-based therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under investigation: Merkel cell carcinoma, RCC, ovarian cancer, gastric cancer, NSCLC, UC</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Fully human IgG1</td>
<td>CTLA-4</td>
<td>FDA approved: melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Under investigation: SCLC, prostate cancer, glioblastoma, SCCA of lung</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>Fully human IgG2</td>
<td>CTLA-4</td>
<td>Under investigation: NSCLC, HNSCC, melanoma, UC</td>
</tr>
</tbody>
</table>

*a*Under investigation’ section for all agents includes tumor type information specific to only phase III studies.

CTLA-4, cytotoxic T-lymphocyte associated antigen; CRC, colorectal carcinoma; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; MM, multiple myeloma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-1 ligand 1; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SCCA, squamous cell carcinoma; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.
phase III study (NCT01668784, CheckMate 025) of patients with aRCC who had received ≥1 prior regimens of antiangiogenic therapy (N = 821); median OS was 25.0 months (95% CI 21.8–NR) with nivolumab versus 19.6 months (95% CI 17.6–23.1) with everolimus (Figure 2). The hazard ratio (HR) for death with nivolumab versus everolimus was 0.73 (98.5% CI 0.57–0.93; \( P = 0.002 \)) [14]. ORR was also significantly higher with nivolumab versus everolimus (25% versus 5%; 95% CI 3.68–9.72, \( P < 0.001 \)). Median duration of response was 12.0 (range 0–27.6) months [14].

Nivolumab demonstrated a favorable toxicity profile versus everolimus in CheckMate 025. Any grade treatment-related AEs occurred in 79% (319 of 406) of patients treated with nivolumab and in 88% (349 of 397) treated with everolimus. Grade 3/4 treatment-related AEs occurred in 19% (76 of 406) and 37% (145 of 397) of patients treated with nivolumab or everolimus, respectively. The most common treatment-related AEs during nivolumab therapy were fatigue (33%; 134 of 406), nausea (14%; 57 of 406) and pruritus (14%; 57 of 406). The most common grade 3/4 treatment-related AE was fatigue (2%; 10 of 406). No treatment-related deaths occurred with nivolumab, whereas two occurred with everolimus [14].

CheckMate 025 also measured patients’ quality of life (QoL) using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) questionnaire. The FKSI-DRS is validated in patients with aRCC, comprising nine symptom-specific questions regarding lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fevers and hematuria [34]. Median changes from baseline in FKSI-DRS questionnaires from CheckMate 025 indicated that nivolumab compared with everolimus treatment resulted in rapid, significant and sustained improvement in health-related QoL [35].

Management of toxicity with ICI treatment

Immune checkpoint inhibition is associated with a unique spectrum of AEs related to imbalances in immunologic tolerance consequent to unchecked immune responses. Immune-mediated or immune-related AEs (irAEs) can involve virtually any organ, with toxicities including reports of endocrinopathies, diarrhea/colitis, dermatitis, hepatitis, pneumonitis and interstitial nephritis [24, 36]. These irAEs are often mild and transient, but can occasionally be moderate or severe, and prolonged. Onset of irAEs can be unpredictable, and continuous vigilance for symptoms of irAEs is recommended [36]. In general, management of moderate or severe irAEs requires interruption of the checkpoint inhibitor and application of immune-modulating medications such as corticosteroid immunosuppression with a prolonged taper over a minimum of 4 weeks (Table 3) [21, 36]. Patients not responding to intravenous corticosteroids after ~72 h should be administered selective immunomodulatory agents such as infliximab or mycophenolate [36].

Pseudoprogression or tumor flare

Specific tumor response patterns with ICI treatment sometimes differ from those with antiangiogenic or tumor cell-targeted therapies. Due to immune-mediated mechanisms of action, ‘tumor flare’ (resulting in increases in size of baseline lesions, development of new lesions and an overall increase in apparent total tumor burden) may occur before cellular immune responses have a chance to affect the actual tumor size [37]. Additionally, transient immune cell infiltration at the tumor site may give the appearance of tumor growth [37, 38]. Tumor flare can confuse tumor response interpretation by appearing as disease progression (hence the term ‘pseudoprogression’) and may result in inappropriately switching therapy before ongoing clinical benefits manifest on imaging [38]. While pseudoprogression is relatively uncommon (occurring in <10% of patients) versus true progression, it sometimes presents a challenge for patients and for clinicians in determining when to stop and/or switch therapy [38]. Additional monitoring of patients either on or off treatment
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Grade/ severity</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>1</td>
<td>Continue immunotherapy&lt;br&gt;Administer topical corticosteroids&lt;br&gt;Oral antihistamines for pruritus</td>
<td>If symptoms develop, treat as higher grade</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Administer oral prednisone 1 mg/kg/day or equivalent&lt;br&gt;Oral antihistamines for pruritus</td>
<td>If symptoms improve, taper steroids over ≥1 month</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>Withhold immunotherapy (grade 3) or permanently discontinue (grade 4)&lt;br&gt;Oral prednisone 1–2 mg/kg/day or equivalent&lt;br&gt;Oral antihistamines for pruritus</td>
<td>If rash does not improve after 12 weeks from last dose of therapy, discontinue immunotherapy&lt;br&gt;If worsens in 48 h, consider additional immunosuppression or supportive measures if no improvement ≥12 weeks from last dose of therapy discontinue immunotherapy</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1</td>
<td>Continue immunotherapy if asymptomatic&lt;br&gt;Monitor liver function tests until resolution</td>
<td>If liver function tests worsen or symptoms develop, treat as higher grade</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Withhold immunotherapy&lt;br&gt;Oral prednisone 1 mg/kg/day or equivalent&lt;br&gt;Monitor liver function tests daily</td>
<td>If liver function tests worsen, treat as higher grade</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>Permanently discontinue therapy&lt;br&gt;i.v. methylprednisolone 2–4 mg/kg/day or equivalent&lt;br&gt;Monitor liver function tests daily</td>
<td>If no response within 3 days, consider additional immunosuppression such as anti-TNF therapy</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>Continue immunotherapy&lt;br&gt;Monitor for symptoms every 3 days</td>
<td>If symptoms develop, treat as higher grade</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Withhold immunotherapy until resolution&lt;br&gt;Monitor for symptoms daily</td>
<td>If persistent beyond 3 days discontinue immunotherapy</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Permanently discontinue immunotherapy&lt;br&gt;Hospitalization (methylprednisolone 2–4 mg/kg/day or equivalent&lt;br&gt;Prophylactic antibiotics</td>
<td>If symptoms worsen in 48 h, consider additional immunosuppression such as anti-TNF therapy</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>1</td>
<td>Follow American Dietary Associations colitis diet and antidiarrheal medications</td>
<td>If symptoms worsen or persist for ≥3 days, rule out infectious cause, withhold immunotherapy, antiarrheal medications, intervention with oral corticosteroids oral corticosteroids; perform endoscopic or radiologic evaluation to confirm the diagnosis</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>For colitis of ≥5 days duration or that recurs, administer corticosteroids at a dose of 0.5–1 mg/kg/day prednisone equivalents followed by corticosteroid taper&lt;br&gt;Withhold immunotherapy</td>
<td>If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1–2 mg/kg/day prednisone equivalents</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Hospitalize for i.v. corticosteroids (methylprednisolone 1–2 mg/kg total daily dose) followed by steroid taper and additional immunosuppression with anti-TNF therapy&lt;br&gt;Withhold immunotherapy (single-agent immunotherapy) or permanently discontinue (combination with checkpoint inhibitor)</td>
<td>If i.v. corticosteroids are not effective within the first 3 days, consider anti-TNF therapy if symptoms persist, anti-TNF therapy may be repeated 2 weeks after the initial dose</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Hypophysitis</td>
<td>Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper</td>
<td>If symptoms worsen in 48 h, consider additional immunosuppression such as anti-TNF therapy</td>
</tr>
<tr>
<td></td>
<td>2/3</td>
<td>Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents and hormone replacement therapy, as clinically needed&lt;br&gt;Withhold immunotherapy</td>
<td>If symptoms worsen or persist for ≥3 days, rule out infectious cause, withhold immunotherapy, antiarrheal medications, intervention with oral corticosteroids oral corticosteroids; perform endoscopic or radiologic evaluation to confirm the diagnosis</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate to severe cases&lt;br&gt;Permanently discontinue immunotherapy</td>
<td>If symptoms worsen or persist for ≥3 days, rule out infectious cause, withhold immunotherapy, antiarrheal medications, intervention with oral corticosteroids oral corticosteroids; perform endoscopic or radiologic evaluation to confirm the diagnosis</td>
</tr>
</tbody>
</table>
with ICIs after Response Evaluation Criteria in Solid Tumors (RECIST) progression has shown subsequent benefits in tumor reduction in patients with metastatic melanoma receiving ipilimumab, leading to the establishment of immune-related response criteria; these represent a distinct approach to capturing additional response patterns in patients benefitting from immune therapy [37]. Practical applications of these recommendations include the following:

1. Tumor assessment should be delayed until 12 weeks of therapy in patients without symptoms of disease progression.
2. In patients with RECIST/World Health Organization-defined disease progression who are either asymptomatic or show stable performance status, no significant deterioration of laboratory values, moderate growth on physical exam or radiographic imaging, and symptomatic improvement in association with a mixed response, disease progression should be confirmed with a repeat scan at least 4 weeks apart.

Treatment beyond progression in aRCC

In the phase II study (NCT01354431) of nivolumab in patients with previously treated aRCC, nivolumab therapy was permitted after first RECIST v1.1 progression if clinical benefit was observed and patients continued to tolerate study therapy. In all, 69% (25 of 36) of patients selected to be treated beyond initial progression (per RECIST v1.1) experienced subsequent tumor reduction or stabilization in target lesion size [39].

In the phase III CheckMate 025 study, nivolumab therapy was also permitted after first RECIST v1.1 progression if clinical benefit was observed and patients continued to tolerate study therapy. In total, 48% (153 of 316) of patients who progressed were treated beyond progression with nivolumab for 4 weeks after first progression. Of 142 patients with tumor measurements before and after progression, 14% (n = 20) had ≥30% tumor burden reduction from first progression [40].

However, the impact of continued therapy on these changes versus patient selection and/or delayed effect of prior therapy, and the accuracy of tumor measurements in this setting, remain to be determined. Although methodologies differed sufficiently to preclude direct comparisons of the outcomes, a reanalysis of CheckMate 025 data by the FDA showed that only five patients (2.9% of 171 patients treated beyond radiographic progression) achieved a PR following an initial RECIST-defined progression [41].

Based on the analyses described above, it is unclear whether responses after RECIST progression represent true cases of pseudoprogression. Identification of pseudoprogression and the role of additional therapy need further exploration in prospective trials.

Patient selection for optimal response with ICIs

PD-L1 expression

Similar to other tumor types, the predictive role of PD-L1 expression by either tumor cells or immune cells in the microenvironment on ICI treatment outcomes in patients with aRCC is, at present, unclear [42].

Subgroup analysis of phase I data for atezolizumab in patients with aRCC indicated trending toward lower antitumor activity (PFS and OS) in patients with low-to-no tumor and tumor infiltrating immune cell PD-L1 expression (<1%, n = 22) compared with patients with PD-L1 expression of ≥1% (n = 33). One-year OS rates were similar across subgroups, but 2-year OS rates tended to be higher for patients with PD-L1 expression ≥1% versus <1% (65%; 95% CI 45%–86% versus 51%; 95% CI 27%–74%, respectively) [27]. Updated analyses confirmed the
association between high PD-L1 expression [HR, 0.62 (0.3–1.28)] and improved OS with atezolizumab treatment [43].

In CheckMate 025, 370 of 410 patients (90%) in the nivolumab group had quantifiable tumor PD-L1 status. Tumor PD-L1 expression ≥/1% was not found to be a marker of nivolumab treatment benefit in aRCC. Regardless of tumor PD-L1 expression, patients experienced survival benefits from nivolumab treatment compared with everolimus. Subgroup analysis of nivolumab-treated patients based on tumor PD-L1 expression showed that response rates were higher in patients with tumors showing ≥1% PD-L1 expression versus tumors expressing <1% PD-L1. However, these patients had a lower median OS (median OS ≥1% versus <1% PD-L1 expression, 21.8 months [95% CI 16.5–28.1] versus 27.4 months [95% CI 21.4–NR], respectively), possibly indicating the more aggressive nature of tumors expressing PD-L1 in RCC [14]. This is consistent with reports where increased PD-L1 expression (H-scores >55) was associated with shorter survival in patients with metastatic RCC treated with the VEGF-targeted therapies pazopanib and sunitinib (median 15.1 versus 35.6 and 15.3 versus 27.8 months, respectively, \( P = 0.03 \)) versus those with lower PD-L1 expression [44]. Interestingly, recent hypothesis-generating data from a small set of PD-L1-expressing tumor samples from patients with aRCC treated with anti-PD-1 therapy suggest that variations in expression of immunoregulatory and metabolic genes may potentially be helpful in selecting patients who are unlikely to benefit from treatment [45]. The prospective exploratory study 009 (\( N = 91 \)) also identified immunomodulatory effects of PD-1 inhibition across nivolumab doses, including increases in tumor-associated lymphocytes, transcriptional changes and chemokine level increases from baseline [46]. Further studies are warranted before the predictive role of such biomarkers in aRCC can be determined.

**Patient baseline characteristics**

Based on available data, clinical benefits observed with ICIs in patients with aRCC seem to be independent of baseline disease characteristics. Nivolumab showed OS benefit over everolimus across all patient subgroups examined in CheckMate 025, including Memorial Sloan Kettering Cancer Center (MSKCC) risk group, prior therapy with sunitinib or pazopanib and number of prior antiangiogenic therapies [14, 47, 48]. Surprisingly, given that mTOR inhibitors are considered most effective in patients with poor prognosis, patients with poor MSKCC prognostic factors appeared to fare better with nivolumab relative to everolimus [14, 34, 47].

Atezolizumab has demonstrated an ORR of 22% in patients with tumors with high Fuhrman grade and/or sarcomatoid features versus 15% in the overall metastatic RCC study population [27, 49], suggesting that more aggressive tumors might be better recognized by the immune system. These data, however, require independent and prospective validation.

**Integration of ICIs into standard practice**

**Comparison of approved second-line agents**

Experience to date with ICIs suggests we are entering a new era in disease management. While significant improvements in PFS and ORR have been demonstrated in phase III studies with antiangiogenic and mTOR inhibitor therapies, statistically significant OS benefit in patients with aRCC following VEGFR TKI therapy had not been reported until recent studies with new drug treatments [14, 50, 51].

Nivolumab was the first approved agent to show a significant OS benefit in patients with aRCC whose disease has progressed following antiangiogenic therapy compared with a comparator agent (everolimus) [14]. This OS benefit was accompanied by better QoL outcomes without compromising safety and tolerability [14]. Nivolumab responses were relatively durable, with approximately one-third of patients alive at 4 years in early studies [32].

Phase III studies of everolimus versus best supportive care, temsirolimus versus sorafenib, and axitinib versus sorafenib in patients with aRCC have reported ORRs of 1.8% versus 0%, 8% versus 8% and 19% versus 9%, respectively [14, 50], but with no significant differences in median OS in previously treated patients.

Cabozeantinib has recently shown significantly longer OS compared with everolimus in a phase III study involving patients with aRCC whose disease progressed following ≥1 VEGFR TKI [7]. Median OS was 21.4 months (95% CI 18.7–NR) with cabozeantinib and 16.5 months (14.7–18.8) with everolimus [HR 0.66 (95% CI 0.53–0.83); \( P = 0.00026 \)] [51]. The OS benefit of cabozeantinib versus everolimus was associated with higher dose reductions due to AEs (60% versus 25% of patients) and a higher incidence of grade 3/4 AEs (68% versus 58%) [7].

Lenvatinib as monotherapy and in combination with everolimus has shown a PFS benefit over everolimus alone in patients with aRCC who progressed after one previous VEGF-targeted therapy. In a randomized phase II study, lenvatinib with everolimus significantly prolonged PFS versus everolimus alone [median PFS 14.6 months (95% CI 5.9–20.1) versus 5.5 months (3.5–7.1), respectively; HR 0.40, 95% CI 0.24–0.68; \( P = 0.0005 \)]. Patients receiving lenvatinib alone had a median PFS of 7.4 months, which although numerically shorter than that of the combination, was not statistically different given the small sample size [(95% CI 5.6–10.2); HR 0.66, 95% CI 0.30–1.10; \( P = 0.12 \)] [9], and did not translate into a statistically significant improvement in OS.

**Future directions**

Several studies are ongoing in patients with aRCC with combinations of ICIs with different targets, for example, anti-PD-1 or PD-L1 and anti-CTLA-4 (Table 4) [42, 52], allowing dual/multifaceted manipulation of immunosuppression. This approach has demonstrated clinically effective synergy from nivolumab plus ipilimumab treatment in patients with advanced melanoma [53]; followed by success in patients with treatment-naïve or previously treated RCC (CheckMate 016 study) with an ORR of about 40% [54]. These provided rationale for a phase III trial comparing this combination with sunitinib in treatment-naïve patients (CheckMate 214, NCT02231749).

Emerging evidence suggests that antiangiogenic therapies may have immune-modulatory effects in addition to their known direct antiangiogenic effects, possibly potentiating the effectiveness of checkpoint inhibitors when administered concurrently.
Based on this rationale, several clinical studies are ongoing in patients with aRCC with combinations of ICIs and VEGF pathway inhibitors, which should help establish the utility of a combination approach versus sequential antiangiogenic therapy and checkpoint blockade (Table 4) [42, 52]. While a few of these combinations have produced unacceptable hepatic toxicity [56, 57], the use of combinations of PD-1 pathway inhibitors with more selective inhibitors of the VEGF pathway (e.g. atezolizumab with bevacizumab, pembrolizumab with axitinib or avelumab with axitinib) have proved to be more tolerable [58–62].

Preliminary results from studies combining immune checkpoint and VEGF pathway inhibitors have shown encouraging clinical activity in terms of PFS and ORR [57–60]. In an ongoing phase Ib study of 52 treatment-naïve patients, pembrolizumab plus axitinib resulted in an ORR of 67%, including two complete responses and 33 PR; median PFS is not yet mature, with seven patients of 11 enrolled in the dose-finding phase remaining progression-free at 11 months [58]. Smaller phase I studies evaluating avelumab plus axitinib and pembrolizumab plus pazopanib combination therapy reported ORRs of 83% (five PRs of six treated patients) and 60% (six of 10 patients; pazopanib 800 mg cohort), respectively [31, 59]. Atezolizumab plus bevacizumab combination therapy in 10 previously untreated patients with mRCC also resulted in clinical benefit (four patients with PRs and four with stable disease) [60]. Confirmatory randomized phase III trials comparing sunitinib versus either atezolizumab with bevacizumab (NCT02420821), avelumab with axitinib (NCT02684006) or pembrolizumab with axitinib (NCT02853331) are ongoing.

Studies are also underway to determine the feasibility of ICIs as neoadjuvant (nivolumab, NCT02575222, NCT02595918; durvalumab with or without tremelimumab, NCT02762006) or adjuvant therapy (nivolumab; NCT02595944, NCT02388906, NCT02743494, NCT02632409; pembrolizumab, NCT02362594, NCT02504372; atezolizumab, NCT02450331, NCT02927301, NCT02912559, NCT02486718).

**Vision for 2020**

Several questions should be addressed to optimize use of ICIs in patients with aRCC: What is the optimal stage of disease and sequence in which to use different therapeutic agents? Will ICIs be effective as first-line treatment? In the adjuvant setting, what degree of cancer burden is required for an immune effect to occur? Should checkpoint inhibitors be given before surgical removal of the primary tumor and/or draining lymph nodes?

More information is required to enable individualization of patient therapy by identification of predictive factors for response to ICI therapy, including tumor tissue biomarkers, circulating microenvironmental factors reflecting cancer mutational burden and germline markers to help identify patients potentially prone to specific toxicities. In tumors other than RCC, the PD-L1 marker has been less predictive when ICIs are given in combination versus monotherapy [63].

The optimal duration of therapy with ICIs must be explored more thoroughly to provide information on when to stop

### Table 4. Combination therapies ongoing with immune checkpoint inhibitors for aRCC

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Registered study</th>
<th>Phase</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combinations of immune checkpoint inhibitors</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nivolumab with ipilimumab</td>
<td>NCT01472081</td>
<td>I</td>
<td>Previously treated and untreated mRCC</td>
</tr>
<tr>
<td>Nivolumab with ipilimumab</td>
<td>NCT02210117</td>
<td>Pilot, randomized</td>
<td>mRCC eligible for cytoreductive nephrectomy, metastasectomy or post-treatment biopsy</td>
</tr>
<tr>
<td>Nivolumab with ipilimumab</td>
<td>NCT02231749</td>
<td>III</td>
<td>Previously untreated a/mRCC</td>
</tr>
<tr>
<td>Pembrolizumab with ipilimumab</td>
<td>NCT02089685</td>
<td>I/II</td>
<td>Previously treated aRCC, treatment naive or treated advanced melanoma</td>
</tr>
<tr>
<td>Durvalumab with tremelimumab</td>
<td>NCT01975831</td>
<td>I</td>
<td>Advanced solid tumors including RCC, non-triple negative breast, ovarian, colorectal, and cervical cancer</td>
</tr>
<tr>
<td><strong>Combinations of immune checkpoint inhibitors with VEGF inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab with sunitinib or pazopanib</td>
<td>NCT01472081</td>
<td>I</td>
<td>Previously treated and untreated mRCC</td>
</tr>
<tr>
<td>Nivolumab with bevacizumab</td>
<td>NCT02210117</td>
<td>Pilot, randomized</td>
<td>mRCC eligible for cytoreductive nephrectomy, metastasectomy or post-treatment biopsy</td>
</tr>
<tr>
<td>Pembrolizumab with axitinib</td>
<td>NCT02853331</td>
<td>III</td>
<td>Untreated aRCC</td>
</tr>
<tr>
<td>Pembrolizumab with axitinib</td>
<td>NCT02133742</td>
<td>Ib</td>
<td>Previously untreated aRCC</td>
</tr>
<tr>
<td>Pembrolizumab with bevacizumab</td>
<td>NCT02348008</td>
<td>I/II</td>
<td>First- and second-line mRCC</td>
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<tr>
<td>Pembrolizumab with pazopanib</td>
<td>NCT02014636</td>
<td>I</td>
<td>aRCC</td>
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<tr>
<td>Atezolizumab with bevacizumab</td>
<td>NCT02420821</td>
<td>III</td>
<td>Untreated aRCC</td>
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<td>Atezolizumab with bevacizumab</td>
<td>NCT01984242</td>
<td>II</td>
<td>Untreated aRCC</td>
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<td>Avelumab with axitinib</td>
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<td>III</td>
<td>Untreated aRCC</td>
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<tr>
<td>Avelumab with axitinib</td>
<td>NCT02493751</td>
<td>I</td>
<td>Untreated aRCC</td>
</tr>
</tbody>
</table>

aRCC, advanced renal cell carcinoma; mRCC, metastatic renal cell carcinoma; VEGF, vascular endothelial growth factor.
treatment in a responsive patient and when to continue treatment in a patient with disease progression.

Answering these questions will affect cost/benefit considerations, especially identification of patients who are unlikely to show early benefit from therapy and decisions on optimal duration of therapy. The potential for a less intense maintenance regimen also needs to be investigated.

At present, these are unanswered questions. Only prospective clinical trials will help to guide appropriate use of ICIs in RCC compared with, or in addition to, targeted agents and other agents.

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