Provisional chapter

Immunotherapy for Renal Cell Carcinoma

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Additional information is available at the end of the chapter

Abstract

Despite the rapid development of therapeutic modalities for advanced or metastatic renal cell carcinoma (mRCC) over the past decade to include traditional immunotherapy, such as high-dose interleukin-2 and interferon-α, as well as a number of targeted anti-angiogenic therapies, mRCC continues to be associated with poor prognosis. Currently, immunotherapy has seen tremendous development in the form of immune checkpoint inhibition and vaccines at a dizzying pace, which are being studied in mRCC and are showing promise as important steps in the management of this disease. With so many drugs available to clinicians and patients, properly integrating immunotherapy especially immune checkpoint blockade (ICB) into the treatment paradigm is challenging. Emerging research with additional ICB agents and novel combination strategies is likely to further impact clinical decision-making. The further development of biomarkers for predicting a response is required to achieve optimal efficacy with these therapeutic interventions. This chapter summarizes the current landscape of standard and emerging immune therapeutics and other modalities for mRCC.

Keywords: immunotherapy, renal cell carcinoma, immune checkpoint inhibitors

1. Introduction

Renal cell carcinoma (RCC) is the most prevalent kidney cancer, with nearly 63,990 cases diagnosed and 14,400 deaths in 2017 [1]. Approximately 25–30% of cases are metastatic at diagnosis [2] and 20–30% of patients who undergo surgical management for local RCC show metastases [3]. Recently, the enhanced comprehension of RCC pathogenesis led to the development of von Hippel-Lindau/ hypoxia-inducible factor (VHL/HIF) targeted therapy as the mainstay of therapeutic options for advanced RCC patients, improving the survival rates of patients [4].

However, the current 3-year overall survival rate is yet no more than 40% and a majority of patients will die because of the progressed disease [5]. As a consequence, new targets and therapies are needed to improve patient outcomes. The rapidly evolving field of immuno-oncology yields several novel immunotherapeutic agents. Currently, cancer vaccines, adoptive T-cell therapy, and immune checkpoint inhibitors (ICIs) are being investigated in advanced RCC and are producing durable responses and noteworthy overall survival improvement. This chapter mainly introduces the treatment landscape of immune therapeutics for RCC.

2. Immunotherapy

The immune system interacts intimately with tumors over the entire disease process. The complex crosstalk between the immune system and cancer cells determines the eventual outcome, either inhibiting or enhancing tumor development [6]. First, antigen-presenting cells (APCs), primarily dendritic cells (DCs), must encounter tumor-associated antigen (TAA), which can emerge via the altered protein structure caused by somatic mutations or differentially expressed proteins. The antigen expression pattern needs to be different from that on normal cells to avoid immune tolerance. APCs process TAA into peptide fragments, which then form a complex with major histocompatibility complex (MHC) class I and II molecules. The initial step of T-cell activation is the recognition of antigen presented on the MHC molecule of APCs by T-cell receptor (TCR). Full T-cell activation also requires a co-stimulatory signal by the binding of CD28 on T cell to B7 ligands (CD80 and CD86) on APCs [7].

Multiple feedback mechanisms exert stimulatory or inhibitory effects on T cells, regulating immune function and preventing an excessive immune response. These mechanisms include immune checkpoint molecules on the surface of T cells and other immune cells such as regulatory T (T_{reg}) cells and myeloid-derived suppressor cells (MDSCs) [8]. Tumor cells can take advantage of these mechanisms to prevent a potential anticancer immune response. RCC usually presents prominent immune cell infiltration, including T cells, natural killer (NK) cells, DCs, and macrophages. During early stages, malignant cells can be poor stimulators and become resistant to the innate immune response. Later, progressively growing tumors impair the adaptive immune response by blocking T-cell signal transduction and function [9]. An increased understanding of these processes has enabled the development of immunotherapy for cancer management.

Immunotherapy is defined as excluding cancer by activating the autoimmune response against the tumor rather than by attacking the tumor directly. Immunotherapy can induce long-lasting anticancer responses owing to the generation of antigen-specific immune memory, either through memory T-cells or antibodies. Several crucial steps are needed to mount an initial effective immune response against tumors [10]. Immune checkpoint blockade disrupts negative immune regulations to enhance immune system activity and boost antitumor immune response. Other immunomodulatory therapies such as cytokine therapy and vaccines potentiate co-stimulatory pathways or stimulate the innate immunity or interact with the immune suppressive tumor microenvironment. The past decade has witnessed the emergence of immunotherapy as an exciting treatment option for different malignancies, including RCC. The following sections discuss these in more detail (**Figure 1**).

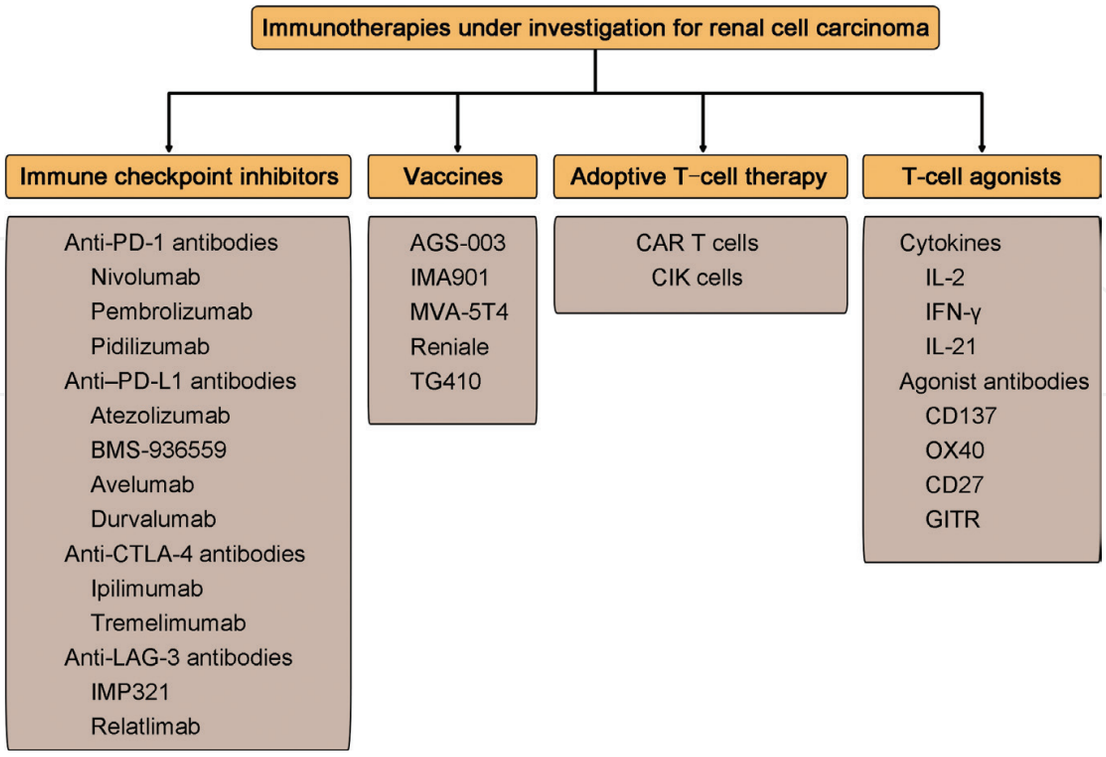

Figure 1. Immunotherapies under investigation for renal cell carcinoma.

3. Traditional immunotherapy for mRCC

Cytokine therapy, involving IFN-α and IL-2, was the main treatment for mRCC before the approval of targeted therapies. IFN-α has antiangiogenic effects, promoting antigen presentation and dendritic cell maturation. The efficacy of IFN-α for mRCC patients was first reported in 1989, and it was confirmed that IFN-α is active [11]. The response rate of IFN-α was 15%, with 3–7 months increase in overall survival [12]. However, most responses to IFN-α were not long-lasting and rare patients showed complete responses. In addition, side effects such as flu-like symptoms and liver toxicity disenabled the long-term use of IFN-α. IL-2 is a potent stimulator of T-cell proliferation and differentiation. High dose IL-2 (HD IL-2) was approved in 1992 for treatment of mRCC based on an objective response rate (ORR) between 10 and 20%; many of the responses were durable and continued for a long time [13]. Despite HD IL-2 having become the preferred treatment, there is a limitation of severe toxicity that can prove in various organ systems, most significantly the heart, lungs, kidney, and central nervous system. The treatment of cytokine alone has gradually fallen out of favor from the first-line setting in the current era of targeted therapy and immunotherapy.

4. Vaccines

Studies on vaccine therapies in mRCC are still ongoing. They mainly focus on the treatment of primary tumors rather than prevention. Tumor vaccines have been designed to enhance the

ability of the immune system to recognize tumor antigens, improve immune microenvironment, and trigger strong specific antitumor cell immunity. Currently, clinical trials evaluating various vaccines have been conducted, although none has demonstrated an improvement in survival thus far. In the future, vaccination approaches will probably be further tailored to the patient's mutanome and tumor-associated antigen profile, with the goal of individualizing treatments and, thus, maximizing the potential benefits [14–16].

4.1. AGS-003

AGS-003 is a dendritic cell immunotherapeutic vaccine constructed from autologous blood dendritic cells and generated through the electroporation of tumor-derived RNA and CD40 ligands (CD40L) RNA into host immune cells [17–19]. The tumor RNA-loaded mature dendritic cells present patient tumor-specific antigens in T-cells via MHC I. Meanwhile, the upregulated CD40L promotes the recruitment of $CD8^+$ T-cell through the regional production of IL-12. A phase II study on 21 mRCC patients were treated by a combination therapy of AGS-003 with 1 cycle of sunitinib (4 weeks on, 2 weeks off), followed by AGS-003 immunotherapy until tumor progression or the end of the study. The median progression-free survival (PFS) and overall survival (OS) were 11.2 months and 30.2 months, respectively. Remarkably, OS was more than 5 years in 5 patients (24%), with 2 patients achieving durable responses for more than 5 years. Of 21 patients, 13 (62%) achieved a clinical benefit (9 with a partial response and 4 with stable disease). Treatment with AGS-003 was well tolerated, with injection site reactions as the primary adverse event (AE). Based on these promising results, a randomized multicenter phase III ADAPT trial is currently under way, to determine whether there is an overall survival benefit between AGS-003 and sunitinib in comparison to sunitinib alone in mRCC patients undergoing de-bulking nephrectomy (NCT01582672).

4.2. IMA901

IMA901 is a therapeutic vaccine consisting of nine different HLA class I-binding tumor-associated peptides and one HLA class II-binding tumor-associated peptide. A phase II trial investigating the addition of cyclophosphamide (which reduces the T regulatory cells) to IMA901 showed that pretreatment with cyclophosphamide prolonged the survival of RCC patients compared with IMA901 therapy alone [20]. The majority of adverse events reported were local injection site reactions. A phase III trial comparing sunitinib with or without this vaccine for mRCC was recently completed. Unfortunately, the OS did not differ significantly between the 2 groups [21].

4.3. Modified vaccinia Ankara (MVA-5 T4; TroVax)

MVA-5 T4 was created to stimulate the immune system to destroy cells expressing 5 T4 antigen. The 5 T4 oncofetal antigen is rarely detected in normal adult tissues but is over-expressed in kidney cancer [22–24]. A randomized, double-blind phase III study (TRIST trial) assessed OS and safety in patients with mRCC [25]. Patients were randomized to MVA-5 T4 (n = 365) or placebo (n = 368) in combination with IL-2, IFN-α, or sunitinib. Unfortunately, MVA-5 T4 in

combination with IFN-α, IL-2, or sunitinib as a first-line mRCC therapy did not lead to a significant difference in OS when compared to the arm without MVA-5 T4 (median 20.1 months MVA-5 T4 versus 19.2 months placebo, p = 0.55). The adverse events' profile was also similar between the treatment arms.

4.4. Autologous tumor cell lysate (Reniale)

Principally, autologous tumor cell lysate vaccine active APCs, such as dendritic cells, which stimulate a cytotoxic T lymphocyte response toward tumor-associated antigens, leading to tumor cell destruction [26–28]. Adjuvant treatment with autologous vaccination Reniale (Liponova AG, Hannover, Germany) improved OS in pT3 RCC patients (10-year OS rates: 53.6% in vaccine group versus 36.2% in control group; p = 0.022) in a phase III study [29]. Additional current studies on nonprotein antigens have been limited. There are other ongoing trials involving the DC-based vaccines. Some of the promising ones involve the transduction of a fusion gene construct of GM-CSF and carbonic anhydrase IX into autologous DCs (NCT01826877), DC/RCC fusion cells in combination with pidilizumab (a PD-1 antibody) (NCT01441765), and DCs in combination with cytokine-induced killer cells (NCT00862303).

5. Immune checkpoint inhibitors

Peptides derived from tumor-associated antigens are presented via MHC I and II epitopes to stimulate $CD8^+$ and $CD4^+$ T cells, respectively [30]. The binding of the T-cell receptor (TCR) to the peptide presented by MHC requires further co-stimulatory signals, resulting in the activation of downstream pathways and secretion of cytotoxic molecules, such as granzyme and perforin [31]. Regulatory mechanisms exist to weaken or inhibit immune response, avoiding excessive autoimmune response. These breaks in the immune system are often referred to as "immune checkpoints," including PD-1/PD-L1, CTLA4/CD80, and so on. Immune checkpoint proteins on CTLs cut off co-stimulatory signals after ligand binding and give rise to T-cell anergy and immune suppression. However, immune checkpoint proteins may become dysregulated under tumor settings, typically via an overexpression of inhibitory ligands and receptors [32]. Blocking these immune checkpoint proteins could improve the capability of CTL to mount and maintain an effective T-cell response [32–34].

Over the past decade, immune checkpoint inhibition (ICI) has become a major focus of research given its durable response rates and promising survival benefits in various malignancies. Current ICIs include the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibodies (ipilimumab and tremelimumab), the programmed cell death protein 1 (PD-1) antibodies (nivolumab, pembrolizumab, and pidilizumab), and the programmed cell death protein ligand 1 (PD-L1) antibodies (atezolizumab, BMS-936559, durvalumab, and avelumab) [35] (**Figure 2**). Multiple clinical trials studying the efficacy of these agents on mRCC are being conducted (**Table 1**), among which nivolumab is the only agent approved for the treatment of mRCC by USFDA in 2015 [36].

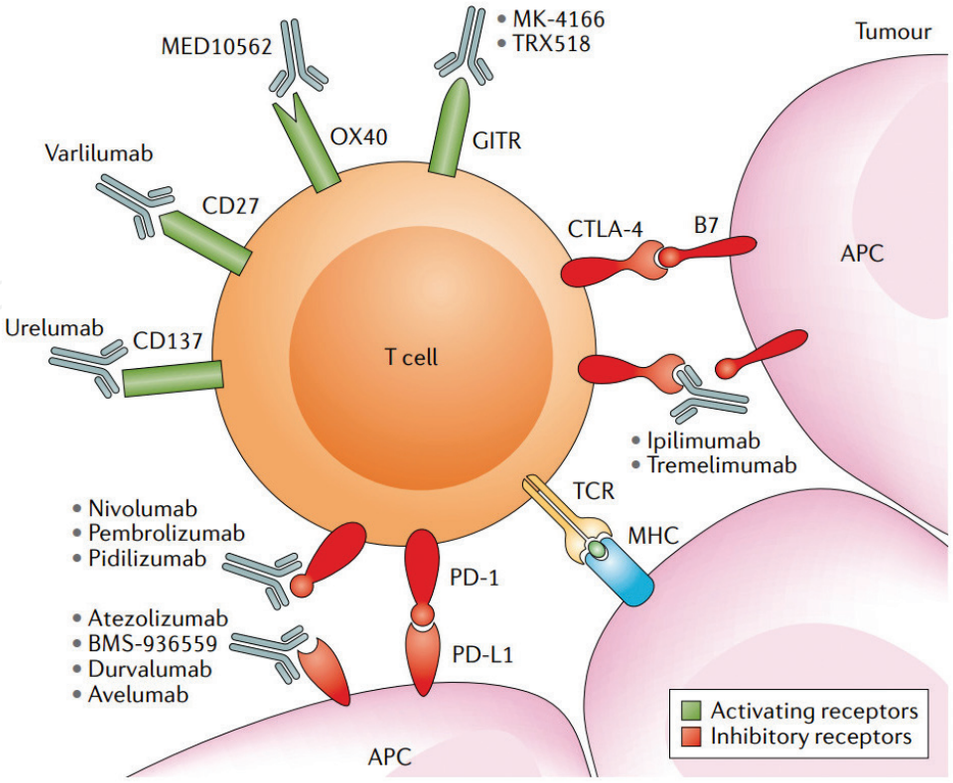

Figure 2. Immune checkpoint inhibitors and agonists being tested in renal cell carcinoma.

Checkpoint inhibitors cause immune-associated adverse events due to hyper-activated T-cell response in healthy tissues. The most common adverse reactions include skin rash, fatigue, and colitis. The incidence and grade of toxicities caused by CTLA-4 antibodies are greater than PD-1/PD-L1-directed monotherapy. Asymptomatic hepatitis and endocrinopathies are also occasionally encountered. Other rare, affected organs include eyes, lungs, kidneys, pancreas, and the hematologic system [37].

T-cell activation is regulated by various co-stimulatory and inhibitory checkpoints. Both agonistic antibodies to activating receptors and blocking antibodies to inhibitory receptors can stimulate T-cell activity and are being tested in advanced renal cell carcinoma and other solid tumors. Activation of T-cells first requires an antigen-presenting cell (APC), such as a dendritic cell, to present an antigen. Here, an APC presents a tumor antigen complexed to major histocompatibility complex (MHC) class I to the T-cell via the T-cell receptor (TCR). Co-stimulatory signals are also needed at this time. At this point, B7 on an APC can bind to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) creating an inhibitory signal, but ipilimumab or tremelimumab—CTLA-4 antibodies—can inhibit the inhibitory signal by binding to CTLA-4 and promote T-cell activation. Once the activated T-cell is in the tumor environment it can recognize the antigen presented by an APC cell in the tumor. At this time, the programmed cell death protein 1 (PD-1) receptor can also send an inhibitory signal to the T-cell when the receptor binds to programmed cell death 1 ligand 1 (PD-L1), which is often expressed on tumor cells. Inhibition of PD-L1 or PD-1 could block that signal. Several PD-1 inhibitors are under investigation for RCC, including pembrolizumab and pidilizumab, and

Agent and trial	Phase	Population	Line	Design	*n*	Response	Toxicities	Comments	Refs
Nivolumab (CheckMate 025/ NCT01668784)	III	Advanced and metastatic RCC Prior systemic therapies: antiangiogenic therapy MSKCC risk group: • favorable: 36% • intermediate: 49% • poor: 15%	Second	Open-label, 1:1 randomized trial Arm A: nivolumab 3 mg/kg every 2 weeks Arm B: everolimus 10 mg every 2 weeks	821	OS (months) • nivolumab: 25 • everolimus: 19 ORR • nivolumab: 25% • everolimus: 5% PFS (months) • nivolumab: 4.6 • everolimus: 4.4	Grade 3–4 treatment-related AEs: • nivolumab: 19% • everolimus: 37%	Hazard ratio for death with nivolumab = 0.73 (P = 0.002)	[36]
NCT01354431	II	Metastatic RCC Prior systemic therapies: Antiangiogenic therapy	Second	Blinded, 1:1 randomized trial Arm A: nivolumab 0.3 mg/kg every 3 weeks Arm B: nivolumab 2 mg/kg every 3 weeks Arm C: nivolumab 10 mg/kg every 3 weeks	168	OS (months) • Arm A: 18.2 • Arm B: 25.5 • Arm C: 24.7 ORR • Arm A: 20% • Arm B: 22% • Arm C: 20% PFS (months) • Arm A: 2.7 • Arm B: 4.0 • Arm C: 4.2	Grade 3–4 treatment-related AEs: • Arm A: 5% • Arm B: 17% • Arm C: 13%	No dose-response relationship was detected as measured by PFS	[46]

Agent and trial	Phase	Population	Line	Design	*n*	Response	Toxicities	Comments	Refs
NCT01358721	Ib	Metastatic RCC Prior systemic therapies: not specified	First, second	Arm A: previously treated group Nivolumab 0.3 mg/kg every 3 weeks Arm B: previously treated group Nivolumab 2 mg/kg every 3 weeks Arm C: previously treated group Nivolumab 10 mg/kg every 3 weeks Arm D: treatment-naive group Nivolumab 10 mg/kg every 3 weeks	91	OS (months) • Arm A: 16.4 • Arm B: NR • Arm C: 25.2 • Arm D: NR ORR • Arm A: 9% • Arm B: 18% • Arm C: 22% • Arm D: 13%	Grade 3–4 treatment-related AEs: • Arm A: 68% • Arm B: 36% • Arm C: 57% • Arm D: 50%	This is the first prospective translational study involving analysis of both baseline and on-treatment biopsies in RCC	Clin Cancer Res 2016;22:5461–71.
Nivolumab and ipilimumab	I	• Previously treated or treatment-naive • All MSKCC risk groups permitted	First, second	Randomized trial of three dosing cohorts: • Arm A: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks × 4 • Arm B: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks × 4 • Arm C: nivolumab 3 mg/kg ipilimumab 3 mg/kg every 3 weeks × 4 All followed by nivolumab 3 mg/kg every 2 weeks until substantial disease progression or toxicity	100	ORR: • ArmA:38% • ArmB:40% PFS at 24 weeks: • ArmA:54% • ArmB:68% Median duration of response: • ArmA: 67 weeks • ArmB: 81 weeks	Treatment in Arm C stopped owing to toxicity Grade 3–4 treatment related AEs: • ArmA:34% • ArmB:64% • ArmC:83%	Median OS not reached with median follow-up duration ranging from 46 to 90 weeks	J. Clin. Oncol. 32:5s (Suppl.), 4504 (2014).

Table 1. Results of immune checkpoint inhibitors in patients with renal cell carcinoma.

nivolumab was recently FDA approved for patients with RCC who have failed prior antiangiogenic therapy. PD-L1 inhibitors under investigation include atezolizumab, BMS-936559, durvalumab, and avelumab. In addition to inhibitory receptors, several activating receptors exist that stimulate T-cell activity, including CD137, CD27, OX40, and GITR. Similarly, several agonist antibodies target these receptors which are under investigation for RCC. These include urelumab targeting CD137, varlilumab targeting CD27, MEDI10562 targeting OX40, and MK-4166 and TRX518 targeting GITR.

5.1. Anti-PD-1 antibodies

PD-1 (CD279) is a cell surface receptor that is expressed on $CD4^+$ and $CD8^+$ T cells as well as NK cells and B cells. The expression of PD-1 is increased by several cytokines, such as IL-2, IL-7, IL-15, and IL-21. PD-1 belongs to the CD28/CTLA-4 superfamily and has an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM) which is able to recruit tyrosine phosphatases, anti-SRC homology phosphatase (SHP)-1 and SHP-2, to modulate inhibitory signaling [38, 39]. When interacting with its ligands, PD-1 suppresses signaling pathways that are involved in T-cell activity [32, 40]. Blockade of PD-1 was evaluated and the initial clinical trial demonstrated impressive antitumor response in several refractory cancer types, including RCC [41]. Thompson and his colleagues examined the expression of PD-1 and PD-L1 in a large number of renal tumors and found PD-1 being expressed in 56% of patient tumors with mononuclear cell infiltration. In addition, PD-1 expression was correlated with advanced tumor stage and worse survival in RCC patients [42–44].

5.1.1. Nivolumab

Nivolumab is a fully human immunoglobulin (Ig) G4 anti-PD-1 monoclonal antibody that selectively inhibits the interaction between PD-1 and its ligands PD-L1 and PD-L2. Several clinical trials of nivolumab have been performed for RCC (**Table 1**). In a phase I study that enrolled 33 patients with mRCC, nivolumab demonstrated an objective response rate of 27% and a manageable safety profile; responses were durable [45]. A phase II study enrolled 168 patients with mRCC who had received previous treatment targeting the vascular endothelial growth factor (VEGF) pathway. Nivolumab was dosed at 0.3, 2, or 10 mg/kg every 3 weeks and showed antitumor activity with no dose-response relationship observed. There was no association between nivolumab dosage and the number of adverse events (AEs), which suggested that the incidence of immune-related AEs was limited [46]. Moreover, a randomized phase III study (Check Mate 025) evaluating nivolumab (3 mg/kg every 2 weeks) versus second-line everolimus (10 mg orally every day, pretreated with antiangiogenic therapy) represented a 5.4-month improvement in median OS (25 months and 19.6 months, respectively). Although the ORR was significantly higher in the nivolumab group than in the everolimus group (25% versus 5%, odds ratio: 5.98 [95% CI, 3.68–9.72], $p < 0.001$), PFS was similar (4.6 versus 4.4 months, HR 0.88 [95% CI, 0.75–1.03], $p = 0.11$). This is the first time that an immune checkpoint inhibitor has demonstrated an OS benefit when compared with patients treated with TKIs for mRCC. The exact mechanism behind the discrepancy between PFS and OS is still unknown, and the authors hypothesized that there might be a potential delayed

benefit in PFS with nivolumab. Nivolumab was very well tolerated, and a lower proportion of patients developed grade 3 or 4 treatment-related AEs (19 and 37%, respectively), including fatigue, nausea, and diarrhea, which suggested that the safety profile of nivolumab was favorable [36]. Nivolumab was approved by the FDA for pretreated advanced clear-cell RCC in November 2015 [36, 41, 46, 47] and is still under investigation as pre- and postoperative therapy in mRCC (ADAPTeR) (NCT02446860) and is also being studied in combination with other drugs (NCT01472081, NCT02231749, NCT02210117, NCT02335918, and NCT02614456).

5.1.2. Pembrolizumab

Pembrolizumab (formerly known as MK3475 or lambrolizumab), a highly selective humanized IgG4 monoclonal antibody against PD-1, has been approved for metastatic melanoma, head and neck cancer, and non-small cell lung cancer (NSCLC) mainly as combinational therapy. Pembrolizumab is currently being investigated in two randomized phase II trials of mRCC patients [48]. A phase I/II study (KEYNOTE-029) involving pembrolizumab plus ipilimumab or pegylated interferon alfa-2b (PEGIFN) in patients with advanced melanoma and RCC reported an acceptable safety profile [49]. Nowadays, several trials evaluating pembrolizumab in combination with various agents with different mechanisms are ongoing (NCT02014636, NCT02133742, NCT02348008, NCT02089685, NCT02501096, NCT02619253, NCT02298959, NCT02646748, NCT02178722, and NCT02475213). The most common adverse events were fatigue, pruritus, and dyspnea. Antitumor activity was observed [50].

5.1.3. Pidilizumab

Pidilizumab (CT-011), another humanized IgG1 kappa monoclonal antibody targeting PD-1, is already under evaluation in several hematologic malignancies, including acute myeloid leukemia (AML), multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia [51]. There are several efforts under way to assess the agent in several solid tumors. As for mRCC, a study is currently under way to assess the combination of pidilizumab with a novel dendritic cell (DC) fusion cell vaccine (NCT01441765). The first group will receive pidilizumab at a dose of 3 mg/kg every 2 weeks intravenously, for a total of 4 cycles. The second group will receive infusions of an autologous DC vaccine during 2–4 cycles of pidilizumab therapy. The noted trial of pidilizumab with an autologous DC vaccine is of substantial interest, especially with emerging vaccine-based therapies, such as AGS-003 and IMA901 [52–54].

5.2. Anti-PD-L1 antibodies

The encouraging results of PD-1 antibodies in cancer management inspired interest in the inhibition of the PD-1 ligands, namely PD-L1. PD-L1 is expressed on a variety of cells, including cancer cells, APCs, T-cells, B cells, and myeloid cells. PD-L1 inhibits T-cell proliferation and adhesion, as well as cytokine production [17, 55, 56]. PD-L1 expression was detected by immune staining in the RCC tissue, and PD-L1 expression by tumor cells (>10%), on infiltrating lymphocytes (>50%), or the composite of both makers was strongly associated with poor prognosis [42, 57].

5.2.1. Atezolizumab

Atezolizumab (MPDL3280A), a fully humanized monoclonal IgG1 antibody against PD-L1, is being evaluated in different cancers, including RCC. It has showed promising results in a multicenter phase I trial involving 17 mRCC patients. The ORR was 12% with responses that lasted for 4–17 months. Seven patients (41%) had stable disease for more than 24 weeks [55]. In another phase Ia study, of the 63 patients with clear-cell RCC that were evaluable, median PFS was 5.6 months and median OS was 28.9 months. The ORR was 15% (18% in patients with >1 and 9% in those with <1% PD-L1 expression) [58].

5.2.2. BMS-936559

BMS-936559 (MDX-1105) is a fully human monoclonal antibody with high affinity to PD-L1 and blocks the binding of PD-L1 to both PD-1 and B7.1. In a phase I trial of evaluating BMS-936559 in 207 patients with different advanced cancer types, 17 patients had mRCC. The study showed that 2 of 17 RCC patients had an objective response with response durations for 4 and 17 months, respectively [59].

5.2.3. Avelumab

Avelumab (MSB0010718C) is a fully human IgG1 monoclonal antibody against PD-L1 and inhibits PD-1-PD-L1 interactions. It also has a native Fc region that could induce antibody-dependent cell-mediated cytotoxicity (ADCC). In a phase Ib, open-label expansion study, avelumab was used in patients with advanced solid tumors and showed an acceptable safety profile [60]. Two ongoing trials evaluate avelumab in combination with axitinib (NCT02493751, NCT02684006).

5.2.4. Durvalumab

Durvalumab (MEDI4736) is another human anti-PD-L1 IgG1 monoclonal antibody. It blocks PD-L1 binding to PD-1 and CD80, with no binding to PD-L2. ADCC and complement-dependent cytotoxicities are removed by an engineered triple mutation in the Fc domain. A Phase 1/2, multicenter, open-label study which evaluated the safety and clinical activity of the drug in patients with multiple solid tumor types such as non-small cell lung cancer noted a very manageable safety profile [61]. There are ongoing trials evaluating durvalumab in combination with other drugs, including tremelimumab (NCT01975831) and MEDI0680 (AMP-514) (a humanized IgG4 monoclonal antibody against PD-1) (NCT02118337) for patients with advanced malignancies including RCC.

5.3. Anti-CTLA-4 antibodies

In addition to the PD-1/PD-L1 checkpoint, CTLA-4, an immune checkpoint on the surface of cytotoxic T-cells, counteracts the action of the co-stimulatory receptor CD28 and plays a key role in the immune response. Both CTLA-4 and CD28 bind identical ligands CD80 and CD86 (called B7-1 and B7-2), but CTLA4 has a higher affinity for both ligands than CD28. Therefore, CTLA4 can antagonize CD28-ligand interactions by competing for ligand binding. In addition,

the interaction of CTLA4 with CD80 or CD86 can lead to the endocytosis of these ligands from the APC surface into a CTLA4-expressing T-cell (a process called trans-endocytosis). The ligand removal impairs the stimulatory capacity of APCs by limiting CD28 signaling and thus inhibits T-cell responses [32, 62]. CTLA-4 antibodies were initially tested on colon adenocarcinoma and sarcoma in mouse models with noted tumor shrinkage [63]. These encouraging results led to the subsequent development of CTLA-4 antibodies, including ipilimumab and tremelimumab.

5.3.1. Ipilimumab

Ipilimumab, an anti-CTLA-4 IgG1 monoclonal antibody, received US FDA approval for the treatment of melanoma in 2011 [64, 65]. It has been investigated as monotherapy plus nivolumab in metastatic melanoma, with the combination treatment being more effective albeit accompanied with significantly more toxicity [66]. Currently, ipilimumab is being investigated in mRCC with the combination of nivolumab. In a phase II study of ipilimumab in patients with mRCC, 1 of 21 patients had a partial response in the lower dose group (3 mg/kg followed by 1 mg/kg every 3 weeks). A total of 5 of 40 patients had partial responses at the higher dose (3 mg/kg every 3 weeks). AEs were highly significant and associated with tumor regression [67]. Ipilimumab has also been investigated in another phase II trial in mRCC; however, just 12% of patients achieved a partial response, with a substantial amount of toxicities [67]. Further phase III trials investigating ipilimumab alone (NCT00057889) and in combination with other drugs have not yet been studied (NCT02231749, NCT02381314).

5.3.2. Tremelimumab

Tremelimumab is another anti-CTLA-4 antibody that is actively being investigated in mRCC. Unlike ipilimumab, it is an IgG2 antibody. It is currently being evaluated with durvalumab in the treatment of patients with mRCC (NCT01975831).

5.4. Anti-LAG-3 antibodies

Lymphocyte activation gene 3 (LAG-3) is expressed on activated T cells and T_{reg}-cells [68]. Upon binding to the MHC class II on APCs, LAG-3 induces an inhibitory signal in T-cells [69], whereas LAG-3 enhances the suppressive function of T_{reg}-cells [70, 71]. Co-expression of LAG-3 and PD-1 is a marker of exhausted T cells and, therefore, the blockade of both receptors confers additive therapeutic activity in preclinical models of chronic infection and cancer [72–74]. In a phase I study, a soluble LAG-3-Ig fusion protein (IMP321), which was designed to stimulate MHC class II-driven DC activation, has been evaluated in patients with advanced RCC. IMP321 induced CD8 T-cell activation in patients and disease stabilization with the absence of toxicity [75]. Currently, a blocking mAb targeting LAG-3 is being tested in the clinic (NCT01968109).

6. Combined therapy

Preclinical studies point out that the dual blockade of PD-1 and CTLA-4 reduced regulatory T_{reg} cell infiltration and increased effector T-cell infiltration and interferon-γ production,

achieving a heightened antitumor effect [76]. This approach has demonstrated clinically effective synergy from nivolumab plus ipilimumab treatment in patients with advanced melanoma [77]. Several studies are ongoing in patients with mRCC on the combinations of ICIs with different targets, for example, anti-PD-1 or PD-L1 and anti-CTLA-4 antibodies [78, 79], allowing dual/multifaceted manipulation of immunosuppression. A combination of nivolumab and ipilimumab has acquired success in patients with treatment naïve or previously treated RCC (CheckMate 016 study) with an ORR of about 40% [80] these provided the 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 such as the enhancement of cytotoxic T-cell trafficking and infiltration in addition to their known direct antiangiogenic effects, possibly potentiating the effectiveness of checkpoint inhibitors when administered concurrently [81]. Based on this rationale, several clinical studies are ongoing in patients with mRCC under the combinations of ICIs and VEGF pathway inhibitors (**Table 2**) [78, 79]. While a few of these combinations have produced unacceptable hepatic toxicity [82, 83], the use of the 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) has proven to be more tolerable [55, 84–87]. Preliminary results from studies combining immune checkpoints and VEGF pathway inhibitors have shown encouraging clinical activity in terms of PFS and ORR [83–86]. In an ongoing phase Ib study of 52 treatment-naïve patients, pembrolizumab plus axitinib resulted in an ORR of 67%, including 2 complete responses and 33 PR; median PFS is not yet mature, with 7 patients of 11 enrolled in the dose-finding phase remaining progression-free at 11 months [84]. Smaller phase I studies evaluating avelumab plus axitinib and pembrolizumab plus pazopanib combination therapy reported ORRs of 83% (5 PRs of 6 treated patients) and 60% (6 of 10 patients; pazopanib 800 mg cohort), respectively [47, 85]. Atezolizumab plus bevacizumab combination therapy in 10 previously untreated patients with mRCC also resulted in clinical benefits (4 patients with PRs and 4 with stable disease) [86]. Confirmatory randomized phase III trials comparing sunitinib versus either atezolizumab with bevacizumab (NCT02420821), avelumab with axitinib (NCT02684006), or pembrolizumab with axitinib (NCT02853331) are ongoing. Preclinical data from an RCC mouse model showed that radiation enhanced the therapeutic effect of IL-2 immunotherapy on pulmonary metastases [88]. One explanation is that DCs are recruited to the irradiated site when radiotherapy is applied in few-fraction and high-dose manners [89]. Currently, a clinical trial evaluating the combination of radiation therapy with pembrolizumab for patients with recurrent or mRCC is ongoing (NCT02318771).

Therefore, a number of combination strategies, such as PD-1/PD-L1 blockade, PD-1 antibody with other immunotherapeutic agents, PD-1 antibody with antiangiogenesis agents, and combination with radiotherapy, are currently in clinical trial research to determine whether there is a most favorable sequence of treatment and if combination strategy benefits mRCC patients. Results from recent clinical trials with immunotherapeutic agents suggest that immunotherapy in combination with other agents is capable of producing durable responses and significant overall survival improvement. Thus, in the future, immunotherapy, together with other treatments, will likely cause a paradigm shift in the clinical management of mRCC patients. However, the combination of immunotherapeutic agents does have considerable

Checkpoint inhibitor	Targeted therapy	Phase	Population	Identifier
Nivolumab	Sunitinib Pazopanib	I	Advanced RCC, prior cytokine therapy allowed	NCT01472081 (CheckMate 016)
Atezolizumab	Bevacizumab	Ib	Untreated, advanced clear cell RCC	NCT01633970
Nivolumab	Bevacizumab	Neoadjuvant pilot	Metastatic clear cell RCC, prior therapy allowed	NCT02210117
Nivolumab	Temsirolimus	Ib/II	Metastatic RCC, prior therapy allowed	NCT02423954
Pembrolizumab	Pazopanib	I/II	Untreated, advanced clear cell RCC	NCT02014636
Pembrolizumab	Axitinib	Ib	Untreated, advanced clear cell RCC	NCT02133742
Pembrolizumab	Bevacizumab	Ib/II	Metastatic clear cell RCC treated with failure of at least one prior therapy	NCT02348008
Pembrolizumab	Aflibercept	I	Metastatic RCC treated with at least one prior VEGF TKI	NCT02298959
Avelumab	Axitinib	Ib	Untreated, advanced clear cell RCC	NCT02493751
Atezolizumab	Bevacizumab	III	Untreated, advanced clear cell RCC	NCT02420821
Avelumab	Axitinib	III	Untreated, advanced clear cell RCC	NCT02684006
Pembrolizumab	Axitinib	III	Untreated, advanced clear cell RCC	NCT02853331 (MK-3475-426/ KEYNOTE-426)

RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Table 2. Ongoing immune checkpoint inhibitor and targeted therapy combinational trials in RCC.

toxicities such as gastrointestinal and hepatic toxicities, and careful patient selection must be guaranteed [90, 91]. Therefore, much more studies must be taken to define the role of combination treatment with immunotherapy agents in mRCC. Moreover, further studies are warranted to identify biomarkers that reliably predict the treatment benefit from these new therapies.

7. Adjuvant and neoadjuvant immunotherapy

With the promising outcome of immunotherapy in mRCC, it is reasonable to explore whether immunotherapy works in the non-metastatic adjuvant setting. Noteworthy, spontaneous antitumor immune infiltration was shown to be higher in primary tumors with respect to matched metastases [92], suggesting that the administration of immunotherapy in the early setting might be more effective than in the advanced setting. However, trials of adjuvant therapy involving tumor cell vaccination, IFN-α, or HD IL-2 have not shown survival benefits [93]. Trials studying the role of checkpoint inhibition (anti PD-1/PD-L1 agents) are proceeding, and the results are eagerly awaited. Studies are also under way 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). We believe that a big movement in RCC management will occur if we can find a way to increase survival rates in the adjuvant or neoadjuvant setting of surgically managed patients.

8. Non-clear cell RCC (nccRCC)

Non-clear cell histology constitutes 20–25% of RCCs [94, 95]. However, this group is heterogeneous, and individually each subtype is relatively rare and thus difficult to study in large prospective trials. nccRCC includes papillary, chromophobe, sarcomatoid, collecting duct, medullary, and various hereditary forms, among which papillary is the most common subtype [94]. Patients with metastatic nccRCC have generally proven to be less responsiveness to the drugs shown to be active in ccRCC [96]. Although some patients with nccRCC may obtain some benefit from VEGF-targeting TKIs, retrospective studies have generally suggested that these agents have inferior efficacy compared with what would be expected in patients with ccRCC [97]. This was also true in the previous era of immunotherapy HD IL-2. Although included in some of the large trials of HD IL-2, patients with nccRCC rarely experienced clinical benefits [95, 98, 99]. Treatment with IFN-α has also showed limited efficacy in patients with non-clear cell histology [95]. No prospective data currently exist to characterize the response of patients with nccRCC to ICIs, though several case reports have been published identifying single responses across various histologies [100–102]. Several ongoing studies are evaluating ICIs as a single agent or in combination in patients with nccRCC.

9. Therapy response and predictive biomarkers

The use of immunotherapies for RCC provides evidence that immune-based treatments can drastically improve survival or antitumor effects for patients with advanced RCC. However, only certain patients obtain clinic benefit as a durable response, so we need to identify reliable predictive biomarkers of treatment response to optimize patient selection.

The evaluation of responses to immunotherapeutic agents represents a challenge in the clinic. Specific tumor response patterns with ICI treatment sometimes differ from those with chemotherapeutic and targeted agents. Due to immune-mediated mechanisms, tumor flare, which shows enlarged size of baseline lesions or increased total tumor burden, may occur before cellular immune responses have a chance to affect the actual tumor size [103]. Additionally, transient immune cell infiltration at the tumor site may boost the appearance of tumor growth [103, 104]. Therefore, 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 [105]. 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 [105]. Recently updated guidelines for the use of modified RECIST (iRECIST) in trials of immunotherapies were published in an effort to standardize and validate these criteria and harmonize the interpretation of the results [106].

Response to ICI has been associated with specific intrinsic and extrinsic properties of tumors or of the host that have been recently classified as the elements of the cancer-immune set point [107]. Intrinsic properties reflect the degree of tumor foreignness [108], linked to the mutational burden and the presence of neoantigens that can be recognized by the immune system, as shown in NSCLC and melanoma [109, 110]. Foreignness of RCC might vary by molecular subtype and a higher number of mutations [111]. In addition, the general individual immune status, mirrored by the levels of circulating lymphocytes and the neutrophil to lymphocyte ratio (NLR), the increase of the C reactive protein, the erythrocyte sedimentation rate PD-L1 expression (although controversial), and LDH were shown to influence the response to ICI.

In addition to the intrinsic properties of the tumors, extrinsic factors, such as exposure to sunlight and to cigarette smoke, the presence of viral infections, and the composition of the gut microbiota, were classified as elements of the cancer-immune set point [107]. The exposure to sunlight and cigarette smoke was relevant for melanoma and NSCLC, respectively, while the presence of viral infections might impact the response to ICI in human papilloma virus positive tumors and Epstein-Barr virus related tumors. Preclinical evidence showed that several bacteroides and bifidobacterium species influenced the efficacy of ICI with anti-CTLA-4 and anti-PD-L1 mAb in mice [112–114]. The role of the gut microbiota in patients with renal cancer treated with ICB requires further investigations.

Taken together, these data suggest that multiple parameters should be taken into account to identify ideal candidates for immunotherapy in RCC. The genomic landscape likely has a role in determining the putative immunogenicity of the tumor [115]; TIL, PD-L1 expression, and immune gene signatures could detect tumors with an inflamed phenotype, which have higher chances of response to ICB [107, 116].

10. Perspective

The advent of immunotherapy has brought about a paradigm shift in the treatment of advanced RCC. Properly integrating immunotherapy into the present treatment is challenging.

Preclinical research has demonstrated the role of VEGF in suppressing tumor immune responses—an attractive strategy to combine with ICIs [117–119]. This successful synergy has been confirmed in phase 1 and 2 studies with axitinib-pembrolizumab [84], axitinib-avelumab [120], lenvatinib-pembrolizumab [121], and bevacizumab-atezolizumab [122, 123]. The ORR ranged between 32% and 67%, and AEs were manageable in all these studies, in contrast to studies in other combinations as TKIs (pazopanib/sunitinib) plus immunotherapy, which did not move forward because of unacceptable toxicity [83, 124, 125]. Although preliminary, the abovementioned results are encouraging and have led to larger, confirmatory, phase 3 trials, which are now actively accruing patients.

In addition, different novel immunotherapies beyond ICIs are being investigated, including adoptive T-cell therapy and T-cell agonists.

Adoptive T-cell transfer therapy refers to the autologous or allogeneic infusion of T-cells. One such therapy involves the generation and infusion of chimeric antigen receptor (CAR) T-cells—T cells that have been genetically modified to express a receptor specific to tumor epitopes independent of HLA. The promising efficacy of anti-CD19 CAR T cells in hematological malignancies has inspired further investigations in solid tumors [126]. One of the key aspects of designing effective CAR T cells is finding a tumor-associated antigen that is uniformly expressed in tumor cells but not in the normal tissue. Carbonic anhydrase 9 (CAIX) is an enzyme that is overexpressed in clear-cell RCC but minimally expressed in normal tissue [127]. Early efforts in using CAIX as a tumor-associated antigen for CAR resulted in liver enzyme elevations that limited its use, likely owing to the therapy also targeting CAIX expressed in the liver bile duct epithelium [128]. Cor H.J. Lamers and his colleagues gave patients a CAIX monoclonal antibody before infusion of CAR T cells to reduce this off-target toxicity [129]. However, in the study, no clinical responses were observed, and the efficacy of CAIX CAR T cells is yet to be proven.

Another form of adoptive immune cell therapy tested in RCC is autologous cytokine-induced killer (CIK) cell immunotherapy. CIK cells are created in vitro by harvesting peripheral mononuclear cells in the blood using an anti-CD3 antibody. The resulting phenotype by IL-1, IFNγ, and IL-2 shares features of effector T-cells and natural killer cells [130]. A phase II trial randomly assigned 148 patients with mRCC to CIK cell immunotherapy or IL-2 combined with IFNα [131]. PFS and OS at 3 years in the CIK cell therapy arm were 18% and 61%, respectively, compared with 12% and 23% in the IL-2 plus IFNα arm ($p = 0.031$ and $p < 0.001$, respectively). This therapy is being further investigated in conjunction with DC vaccines and early results show that therapy is well tolerated and might have activity against RCC [132].

Stimulatory molecules expressed on immune cells can also be targeted with agonist antibodies. CD137 is a co-stimulatory molecule for T-cells that increases T-cell effector activity and survival. Its use in combination with anti-DR5 and anti-CD40 antibodies in mouse models of RCC has shown to improve survival compared with control mice ($p < 0.001$) [133]. The CD137 agonist PF-05082566 is currently being tested in combination with pembrolizumab in a phase I trial of advanced solid tumors, including RCC (NCT02179918). Varlilumab is an agonist antibody targeting CD27, another co-stimulatory molecule for T-cell activation. In a phase I trial in solid tumors, including 11 patients with RCC, of the six evaluable RCC patients, two had stable diseases [134]. This antibody is currently being studied in combination with sunitinib and in combination with atezolizumab in phase I/II trials in RCC (NCT02386111).

In addition to CD137 and CD27, other co-stimulatory molecules such as OX40 and GITR are also promising therapeutic targets. Trials of monotherapy with the OX40 agonist MEDI0562, and with the GITR agonists MK-4166 and TRX518, are under way in solid tumor malignancies (NCT02318394, NCT02132754, and NCT02628574). Like combination checkpoint blockade strategies, much enthusiasm exists for combined treatment strategies with other immunomodulatory agents [135, 136].

Owing to the unique antitumor mechanisms elicited by immunotherapy, patients treated with these agents can have tumor response patterns that are different from conventional tumor-response criteria, such as the WHO criteria [137, 138]. A subset of patients receiving ICI therapy develop pseudoprogression, in which tumor burden decreases after an initial increase or during or after the appearance of new lesions. The evaluation of pseudoprogression provides new challenges in treatment monitoring and therapeutic decision-making because it cannot be evaluated with the existing response-evaluation criteria. The establishment of a standardized strategy to evaluate immune-related responses in patients receiving ICIs is extremely important. However, advances in the knowledge of immune-related responses have been challenged by the fact that only a few clinical trials have used the immune-related response criteria (irRC) [103] or immune-related response evaluation criteria in solid tumors (irRECIST) [139] as the primary criteria to define their end points [77, 104, 140].

In addition, the development of robust biomarkers to assist prediction of response and clinical benefits of immunotherapy is essential to further advance the field as precision immuno-oncology. Despite the remarkable success of clinical applications of immunotherapy reported in the past decade, the effectiveness of these therapies varies greatly across individual patients and among different tumor types. A substantial unmet need is the development of biomarkers of response to immunotherapeutic agents, in order to identify, before the initiation of treatment, which patients are likely to experience clinical benefit from such treatments. This aspect is particularly important in the management of tumors with low response rates, such as NSCLC (response rate ≤ 20%), RCC, and urothelial carcinoma (UCC) [141]. The growing knowledge of molecular subtypes of RCC with next-generation sequencing is the first step toward developing RCC-specific genomic signatures and guiding therapy selection, thereby moving toward precision medicine [142].

Taken together, the therapeutic activity of immunotherapy is the result of a complex interplay between multiple factors in the tumor, tumor microenvironment, and immune system, requiring a collaborative approach to translate the emerging knowledge into the clinical context.

11. Conclusions

Novel immune therapies are emerging as an important addition to targeted therapies in the treatment of RCC. Many questions regarding their use remain to be optimized including dose, schedule, AEs, and adjuvant or neoadjuvant application. An investigation of the rational combination of different treatment modalities is also critical in maximizing the potential of immunotherapy. Additional investigations into predictive biomarkers or resistance mechanisms are

needed to optimize patient selection. To date, nivolumab has been approved in the second-line setting, and randomized phase III trials with novel immunotherapy combinations are challenging the first-line standard of care in RCC—in the near future, immunotherapy will likely be a new standard therapy.

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA: A Cancer Journal for Clinicians. 2017;**67**(1):7-30

[2] Ljungberg B, Campbell SC, Choi HY, et al. Corrigendum to "the epidemiology of renal cell carcinoma" [Eur Urol 2011;60:615-21]. European Urology. 2011;**60**(6):1317

[3] Athar U, Gentile TC. Treatment options for metastatic renal cell carcinoma: A review. The Canadian Journal of Urology. 2008;**15**(2):3954-3966

[4] Iacovelli R, Sternberg CN, Porta C, et al. Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: A systematic review and meta-analysis. Current Drug Targets. 2015;**16**(2):164-170

[5] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. Journal of Clinical Oncology. 2009;**27**(34):5794-5799

[6] Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;**144**(5): 646-674

[7] Chen L. Co-inhibitory molecules of the B7–CD28 family in the control of T-cell immunity. Nature Reviews Immunology. 2004;**4**(5):336-347

[8] Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nature Reviews Immunology. 2009;**9**(3):162-174

[9] Campoli M, Ferrone S, Zea AH, et al. Mechanisms of tumor evasion. Cancer Treatment and Research. 2005;**123**:61-88

[10] Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011; **480**(7378):480-489

[11] Oliver RT, Nethersell AB, Bottomley JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal carcinoma. British Journal of Urology. 1989; **63**(2):128-131

[12] Fossa SD. Interferon in metastatic renal cell carcinoma. Seminars in Oncology. 2000;**27**(2): 187-193

[13] Floros T, Tarhini AA. Anticancer cytokines: Biology and clinical effects of interferon-alpha2, interleukin (IL)-2, IL-15, IL-21, and IL-12. Seminars in Oncology. 2015;**42**(4):539-548

[14] Ophir E, Bobisse S, Coukos G, et al. Personalized approaches to active immunotherapy in cancer. Biochimica et Biophysica Acta. 2016;**1865**(1):72-82

[15] Keenan BP, Jaffee EM. Whole cell vaccines—Past progress and future strategies. Seminars in Oncology. 2012;**39**(3):276-286

[16] Fritsch EF, Hacohen N, Wu CJ. Personal neoantigen cancer vaccines: The momentum builds. Oncoimmunology. 2014;**3**:e29311

[17] Combe P, De Guillebon E, Thibault C, et al. Trial watch: Therapeutic vaccines in metastatic renal cell carcinoma. Oncoimmunology. 2015;**4**(5):e1001236

[18] Figlin RA. Personalized immunotherapy (AGS-003) when combined with sunitinib for the treatment of metastatic renal cell carcinoma. Expert Opinion on Biological Therapy. 2015;**15**(8):1241-1248

[19] Amin A, Dudek AZ, Logan TF, et al. Survival with AGS-003, an autologous dendritic-cell-based immunotherapy, in combination with sunitinib in unfavorable risk patients with advanced renal cell carcinoma (RCC): Phase 2 study results. Journal for Immuno Therapy of Cancer. 2015;**3**:14

[20] Walter S, Weinschenk T, Stenzl A, et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nature Medicine. 2012;**18**(8):1254-1261

[21] Rini BI, Stenzl A, Zdrojowy R, et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): A multicentre, open-label, randomised, controlled, phase 3 trial. The Lancet Oncology. 2016;**17**(11):1599-1611

[22] Kaufman H, Taback B, Sherman W, et al. Phase II trial of Modified Vaccinia Ankara (MVA) virus expressing 5T4 and high dose Interleukin-2 (IL-2) in patients with metastatic renal cell carcinoma. Journal of Translational Medicine. 2009;**7**:2

[23] Amato RJ. 5T4-modified vaccinia Ankara: Progress in tumor-associated antigen-based immunotherapy. Expert Opinion on Biological Therapy. 2010;**10**(2):281-287

[24] Amato RJ, Shingler W, Goonewardena M, et al. Vaccination of renal cell cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) alone or administered in combination with interferon-alpha (IFN-alpha): A phase 2 trial. Journal of Immunotherapy. 2009;**32**(7):765-772

[25] Amato RJ, Hawkins RE, Kaufman HL, et al. Vaccination of metastatic renal cancer patients with MVA-5T4: A randomized, double-blind, placebo-controlled phase III study. Clinical Cancer Research. 2010;**16**(22):5539-5547

[26] Wittke S, Baxmann S, Fahlenkamp D, et al. Tumor heterogeneity as a rationale for a multi-epitope approach in an autologous renal cell cancer tumor vaccine. OncoTargets and Therapy. 2016;**9**:523-537

[27] Matsushita H, Enomoto Y, Kume H, et al. A pilot study of autologous tumor lysate-loaded dendritic cell vaccination combined with sunitinib for metastatic renal cell carcinoma. Journal for ImmunoTherapy of Cancer. 2014;**2**:30

[28] Wang H, Feng F, Zhu M, et al. Therapeutic efficacy of dendritic cells pulsed by autologous tumor cell lysate in combination with CIK cells on advanced renal cell carcinoma. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2015;**31**(1):67-71

[29] May M, Kendel F, Hoschke B, et al. Adjuvant autologous tumour cell vaccination in patients with renal cell carcinoma. Overall survival analysis with a follow-up period in excess of more than 10 years. Urologe A. 2009;**48**(9):1075-1083

[30] Kirkwood JM, Butterfield LH, Tarhini AA, et al. Immunotherapy of cancer in 2012. CA: A Cancer Journal for Clinicians. 2012;**62**(5):309-335

[31] Schwartz RH. A cell culture model for T lymphocyte clonal anergy. Science. 1990; **248**(4961):1349-1356

[32] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews. Cancer. 2012;**12**(4):252-264

[33] Webster RM. The immune checkpoint inhibitors: Where are we now? Nature Reviews. Drug Discovery. 2014;**13**(12):883-884

[34] Byun DJ, Wolchok JD, Rosenberg LM, et al. Cancer immunotherapy—Immune checkpoint blockade and associated endocrinopathies. Nature Reviews. Endocrinology. 2017;**13**(4):195-207

[35] Ghatalia P, Zibelman M, Geynisman DM, et al. Checkpoint inhibitors for the treatment of renal cell carcinoma. Current Treatment Options in Oncology. 2017;**18**(1):7

[36] Motzer RJ, Escudier B, Mcdermott DF, et al. Nivolumab versus Everolimus in advanced renal-cell carcinoma. The New England Journal of Medicine. 2015;**373**(19):1803-1813

[37] Postow MA. Managing immune checkpoint-blocking antibody side effects. American Society of Clinical Oncology Educational Book. 2015;**35**(76):76-83

[38] Nirschl CJ, Drake CG. Molecular pathways: Coexpression of immune checkpoint molecules: Signaling pathways and implications for cancer immunotherapy. Clinical Cancer Research. 2013;**19**(18):4917-4924

[39] Macfarlane AWT, Jillab M, Plimack ER, et al. PD-1 expression on peripheral blood cells increases with stage in renal cell carcinoma patients and is rapidly reduced after surgical tumor resection. Cancer Immunology Research. 2014;**2**(4):320-331

[40] Amarnath S, Mangus CW, Wang JC, et al. The PDL1-PD1 axis converts human TH1 cells into regulatory T cells. Science Translational Medicine. 2011;**3**(111):111ra120

[41] Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates. Journal of Clinical Oncology. 2010;**28**(19):3167-3175

[42] Tykodi SS. PD-1 as an emerging therapeutic target in renal cell carcinoma: Current evidence. OncoTargets and Therapy. 2014;**7**:1349-1359

[43] Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Research. 2006;**66**(7):3381-3385

[44] Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. Clinical Cancer Research. 2007;**13** (2 Pt 2):709s-715s

[45] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England Journal of Medicine. 2012;**366**(26):2443-2454

[46] Motzer RJ, Rini BI, Mcdermott DF, et al. Nivolumab for metastatic renal cell carcinoma: Results of a randomized phase II trial. Journal of Clinical Oncology. 2015;**33**(13):1430-1437

[47] Mcdermott DF, Drake CG, Sznol M, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving Nivolumab. Journal of Clinical Oncology. 2015;**33**(18):2013-2020

[48] Godwin JL, Zibelman M, Plimack ER, et al. Immune checkpoint blockade as a novel immunotherapeutic strategy for renal cell carcinoma: A review of clinical trials. Discovery Medicine. 2014;**18**(101):341-350

[49] Atkins MB, Choueiri TK, Hodi FS, et al. Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): Data from the KEYNOTE-029 phase 1 study. Journal of Clinical Oncology. 2015;**33**(15_suppl):3009-3009

[50] Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clinical Cancer Research. 2015;**21**(19):4286-4293

[51] Berger R, Rotem-Yehudar R, Slama G, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. Clinical Cancer Research. 2008;**14**(10):3044-3051

[52] Reinhardt C, Zdrojowy R, Szczylik C, et al. Results of a randomized phase II study investigating multipeptide vaccination with IMA901 in advanced renal cell carcinoma (RCC). Journal of Clinical Oncology. 2010;**28**(15_suppl):4529-4529

[53] Figlin RA, Nicolette CA, Amin A, et al. Monitoring T-cell responses in a phase II study of AGS-003, an autologous dendritic cell-based therapy in patients with newly diagnosed advanced stage renal cell carcinoma in combination with sunitinib. Journal of Clinical Oncology. 2011;**29**(15_suppl):2532-2532

[54] Amin A, Dudek A, Logan T, et al. A phase II study testing the safety and activity of AGS-003 as an immunotherapeutic in subjects with newly diagnosed advanced stage renal cell carcinoma (RCC) in combination with sunitinib. Journal of Clinical Oncology. 2010;**28**(15_suppl):4588-4588

[55] Weinstock M, Mcdermott D. Targeting PD-1/PD-L1 in the treatment of metastatic renal cell carcinoma. Therapeutic Advances in Urology. 2015;**7**(6):365-377

[56] Gunturi A, Mcdermott DF. Potential of new therapies like anti-PD1 in kidney cancer. Current Treatment Options in Oncology. 2014;**15**(1):137-146

[57] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(49):17174-17179

[58] Mcdermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: Long-term safety, clinical activity, and immune correlates from a phase Ia study. Journal of Clinical Oncology. 2016;**34**(8):833-842

[59] Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England Journal of Medicine. 2012;**366**(26): 2455-2465

[60] Kelly K, Patel MR, Infante JR, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with metastatic or locally advanced solid tumors: Assessment of safety and tolerability in a phase I, open-label expansion study. Journal of Clinical Oncology. 2015;**33**(15_suppl):3044-3044

[61] Rizvi NA, Brahmer JR, Ou S-HI, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2015;**33**(15_suppl):8032-8032

[62] Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. Nature Reviews. Immunology. 2011;**11**(12):852-863

[63] Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 1996;**271**(5256):1734-1736

[64] Lipson EJ, Drake CG. Ipilimumab: An anti-CTLA-4 antibody for metastatic melanoma. Clinical Cancer Research. 2011;**17**(22):6958-6962

[65] Hodi FS, O'day SJ, Mcdermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. The New England Journal of Medicine. 2010;**363**(8):711-723

[66] Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. The New England Journal of Medicine. 2015;**373**(13):1270-1271

[67] Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. Journal of Immunotherapy. 2007;**30**(8):825-830

[68] Huard B, Gaulard P, Faure F, et al. Cellular expression and tissue distribution of the human LAG-3-encoded protein, an MHC class II ligand. Immunogenetics. 1994;**39**(3):213-217

[69] Huard B, Prigent P, Tournier M, et al. CD4/major histocompatibility complex class II interaction analyzed with CD4- and lymphocyte activation gene-3 (LAG-3)-Ig fusion proteins. European Journal of Immunology. 1995;**25**(9):2718-2721

[70] Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in regulatory T cells. Immunity. 2004;**21**(4):503-513

[71] Okamura T, Fujio K, Shibuya M, et al. CD4+CD25-LAG3+ regulatory T cells controlled by the transcription factor Egr-2. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(33):13974-13979

[72] Blackburn SD, Shin H, Haining WN, et al. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nature Immunology. 2009;**10**(1):29-37

[73] Butler NS, Moebius J, Pewe LL, et al. Therapeutic blockade of PD-L1 and LAG-3 rapidly clears established blood-stage Plasmodium infection. Nature Immunology. 2011; **13**(2):188-195

[74] Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Research. 2012;**72**(4):917-927

[75] Brignone C, Escudier B, Grygar C, et al. A phase I pharmacokinetic and biological correlative study of IMP321, a novel MHC class II agonist, in patients with advanced renal cell carcinoma. Clinical Cancer Research. 2009;**15**(19):6225-6231

[76] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(9):4275-4280

[77] Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. New England Journal of Medicine. 2013;**369**(2):122-133

[78] Parekh H, Rini BI. Emerging therapeutic approaches in renal cell carcinoma. Expert Review of Anticancer Therapy. 2015;**15**(11):1305-1314

[79] Aoun F, Kourie HR, Sideris S, et al. Checkpoint inhibitors in bladder and renal cancers: Results and perspectives. Immunotherapy. 2015;**7**(12):1259-1271

[80] Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The CheckMate 016 study. Journal of Clinical Oncology. 2017;**35**(34):3851-3858

[81] Hughes PE, Caenepeel S, Wu LC. Targeted therapy and checkpoint immunotherapy combinations for the treatment of cancer. Trends in Immunology. 2016;**37**(7):462-476

[82] Amin A, Plimack ER, Infante JR, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC). American Society of Clinical Oncology. 2014:5010

[83] Mcdermott D, Infante J, Chowdhury S, et al. 2622 A phase I/II study to assess the safety and efficacy of pazopanib (paz) and pembrolizumab (pembro) in patients (pts) with advanced renal cell carcinoma (aRCC). European Journal of Cancer. 2015;**51**:S519-S520

[84] Atkins M, Plimack E, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients (pts) with advanced renal cell carcinoma (aRCC): Preliminary safety and efficacy results. European Society for Medical Oncology. 2016

[85] Larkin J, Rini B, Nathan P, et al. Phase 1b dose-finding study of avelumab (anti-PD-L1)+ axitinib in treatment-naïve patients with advanced renal cell carcinoma. European Society for Medical Oncology. 2016:775PD

[86] Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nature Communications. 2016;**7**:12624

[87] Atkins MB, Gupta S, Choueiri TK, et al. Phase Ib dose-finding study of axitinib plus pembrolizumab in treatment-naïve patients with advanced renal cell carcinoma. Journal for Immunotherapy of Cancer. 2015;**3**(S2):P353

[88] Chakrabarty A, Hillman GG, Maughan RL, et al. Radiation therapy enhances the therapeutic effect of immunotherapy on pulmonary metastases in a murine renal adenocarcinoma model. In Vivo. 1994;**8**(1):25-31

[89] De Meerleer G, Khoo V, Escudier B, et al. Radiotherapy for renal-cell carcinoma. The Lancet Oncology. 2014;**15**(4):e170-e177

[90] Pal SK, Vogelzang NJ. Sequential treatment strategies and combination therapy regimens in metastatic renal cell carcinoma. Clinical Advances in Hematology & Oncology. 2013;**11**(3):146-155

[91] Buonerba C, Di Lorenzo G, Sonpavde G. Combination therapy for metastatic renal cell carcinoma. Annals of Translational Medicine. 2016;**4**(5):100

[92] Remark R, Alifano M, Cremer I, et al. Characteristics and clinical impacts of the immune environments in colorectal and renal cell carcinoma lung metastases: Influence of tumor origin. Clinical Cancer Research. 2013;**19**(15):4079-4091

[93] Smaldone MC, Fung C, Uzzo RG, et al. Adjuvant and neoadjuvant therapies in high-risk renal cell carcinoma. Hematology/Oncology Clinics of North America. 2011;**25**(4):765-791

[94] Valenca LB, Hirsch MS, Choueiri TK, et al. Non-clear cell renal cell carcinoma, part 1: Histology. Clinical Advances in Hematology & Oncology. 2015;**13**(5):308-313

[95] Motzer RJ, Bacik J, Mariani T, et al. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. Journal of Clinical Oncology. 2002;**20**(9):2376-2381

[96] Zibelman M, Plimack ER. Integrating immunotherapy into the management of renal cell carcinoma. Journal of the National Comprehensive Cancer Network. 2017;**15**(6):841-847

[97] Kroeger N, Xie W, Lee JL, et al. Metastatic non-clear cell renal cell carcinoma treated with targeted therapy agents: Characterization of survival outcome and application of the international mRCC database consortium criteria. Cancer. 2013;**119**(16):2999-3006

[98] Mcdermott DF, Cheng SC, Signoretti S, et al. The high-dose aldesleukin "select" trial: A trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clinical Cancer Research. 2015;**21**(3):561-568

[99] Mcdermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2005;**23**(1):133-141

[100] Adra N, Cheng L, Pili R. Unclassified renal cell carcinoma with significant response to nivolumab. Clinical Genitourinary Cancer. 2017;**15**(3):e517-e519

[101] Beckermann KE, Jolly PC, Kim JY, et al. Clinical and immunologic correlates of response to PD-1 blockade in a patient with metastatic renal medullary carcinoma. Journal for ImmunoTherapy of Cancer. 2017;**5**:1

[102] Geynisman DM. Anti-programmed cell death protein 1 (PD-1) antibody Nivolumab leads to a dramatic and rapid response in papillary renal cell carcinoma with Sarcomatoid and Rhabdoid features. European Urology. 2015;**68**(5):912-914

[103] Wolchok JD, Hoos A, O'day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clinical Cancer Research. 2009;**15**(23):7412-7420

[104] Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. Journal of Clinical Oncology. 2015;**33**(31):3541-3543

[105] Adams S, Diamond JR, Hamilton EP, et al. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). American Society of Clinical Oncology. 2016:1009

[106] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017;**18**(3):e143-e152

[107] Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017;**541**(7637):321-330

[108] Blank CU, Haanen JB, Ribas A, et al. Cancer immunology. The "cancer immunogram". Science. 2016;**352**(6286):658-660

[109] Chan TA, Wolchok JD, Snyder A. Genetic basis for clinical response to CTLA-4 blockade in melanoma. The New England Journal of Medicine. 2015;**373**(20):1984

[110] Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;**348**(6230):124-128

[111] Pena-Llopis S, Vega-Rubin-De-Celis S, Liao A, et al. BAP1 loss defines a new class of renal cell carcinoma. Nature Genetics. 2012;**44**(7):751-759

[112] Vetizou M, Pitt JM, Daillere R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015;**350**(6264):1079-1084

[113] Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science. 2015;**350**(6264):1084-1089

[114] Pitt JM, Vetizou M, Gomperts Boneca I, et al. Enhancing the clinical coverage and anticancer efficacy of immune checkpoint blockade through manipulation of the gut microbiota. Oncoimmunology. 2017;**6**(1):e1132137

[115] Luen S, Virassamy B, Savas P, et al. The genomic landscape of breast cancer and its interaction with host immunity. Breast. 2016;**29**:241-250

[116] Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. Clinical Cancer Research. 2016;**22**(8):1865-1874

[117] Ott PA, Hodi FS, Buchbinder EI. Inhibition of immune checkpoints and vascular endothelial growth factor as combination therapy for metastatic melanoma: An overview of rationale, preclinical evidence, and initial clinical data. Frontiers in Oncology. 2015;**5**:202

[118] Alfaro C, Suarez N, Gonzalez A, et al. Influence of bevacizumab, sunitinib and sorafenib as single agents or in combination on the inhibitory effects of VEGF on human dendritic cell differentiation from monocytes. British Journal of Cancer. 2009;**100**(7):1111-1119

[119] Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nature Reviews. Cancer. 2012;**12**(4):237-251

[120] Choueiri TK, Larkin JM, Oya M, et al. First-line avelumab+ axitinib therapy in patients (pts) with advanced renal cell carcinoma (aRCC): Results from a phase Ib trial. American Society of Clinical Oncology. 2017:4504

[121] Taylor M, Dutcus C, Schmidt E, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients with selected solid tumors. Annals of Oncology. 2016; **27**(suppl_6):776

[122] Mcdermott DF, Atkins MB, Motzer RJ, et al. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). American Society of Clinical Oncology. 2017:431

[123] Sznol M, Mcdermott DF, Jones SF, et al. Phase Ib evaluation of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) in patients (pts) with metastatic renal cell carcinoma (mRCC). American Society of Clinical Oncology. 2015

[124] Rini BI, Vogelzang NJ. Future challenges for drug development in renal cell carcinoma. American Society of Clinical Oncology. 2016

[125] Rini BI, Stein M, Shannon P, et al. Phase 1 dose-escalation trial of tremelimumab plus sunitinib in patients with metastatic renal cell carcinoma. Cancer. 2011;**117**(4):758-767

[126] Kakarla S, Gottschalk S. CAR T cells for solid tumors: Armed and ready to go? Cancer Journal (Sudbury, Mass.). 2014;**20**(2):151

[127] Bui MH, Seligson D, Han K-R, et al. Carbonic anhydrase IX is an independent predictor of survival in advanced renal clear cell carcinoma. Clinical Cancer Research. 2003; **9**(2):802-811

[128] Lamers CH, Sleijfer S, Vulto AG, et al. Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: First clinical experience. Journal of Clinical Oncology. 2006;**24**(13):e20-e22

[129] Lamers CH, Sleijfer S, Van Steenbergen S, et al. Treatment of metastatic renal cell carcinoma with CAIX CAR-engineered T cells: Clinical evaluation and management of on-target toxicity. Molecular Therapy. 2013;**21**(4):904-912

[130] Kim JS, Chung IS, Lim SH, et al. Preclinical and clinical studies on cytokine-induced killer cells for the treatment of renal cell carcinoma. Archives of Pharmacal Research. 2014;**37**(5):559-566

[131] Liu L, Zhang W, Qi X, et al. Randomized study of autologous cytokine-induced killer cell immunotherapy in metastatic renal carcinoma. Clinical Cancer Research. 2012;**18**(6): 1751-1759

[132] Wang D, Zhang B, Gao H, et al. Clinical research of genetically modified dendritic cells in combination with cytokine-induced killer cell treatment in advanced renal cancer. BMC Cancer. 2014;**14**(1):251

[133] Westwood JA, Darcy PK, Guru PM, et al. Three agonist antibodies in combination with high-dose IL-2 eradicate orthotopic kidney cancer in mice. Journal of Translational Medicine. 2010;**8**(1):42

[134] Infante JR, Burris HA, Ansell SM, et al. Immunologic activity of an activating anti-CD27 antibody (CDX-1127) in patients (pts) with solid tumors. American Society of Clinical Oncology. 2014:3027

[135] Sanmamed MF, Pastor F, Rodriguez A, et al. Agonists of co-stimulation in cancer immunotherapy directed against CD137, OX40, GITR, CD27, CD28, and ICOS[C]. Seminars in Oncology. 2015:640-655

[136] Peggs K, Quezada S, Allison J. Cancer immunotherapy: Co-stimulatory agonists and co-inhibitory antagonists. Clinical & Experimental Immunology. 2009;**157**(1):9-19

[137] Miller A, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer. 1981;**47**(1):207-214

[138] Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;**45**(2):228-247

[139] Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: Immune-related response criteria using unidimensional measurements. Clinical Cancer Research. 2013;**19**(14):3936-3943

[140] Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non–small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study. Journal of Clinical Oncology. 2012;**30**(17):2046-2054

[141] Nishino M, Ramaiya NH, Hatabu H, et al. Monitoring immune-checkpoint blockade: Response evaluation and biomarker development. Nature Reviews Clinical Oncology. 2017;**14**(11):655

[142] Posadas EM, Limvorasak S, Figlin RA. Targeted therapies for renal cell carcinoma. Nature Reviews Nephrology. 2017;**13**(8):496-511

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