Published in final edited form as:

BioDrugs. 2014 December ; 28(6): 513–526. doi:10.1007/s40259-014-0111-4.

Harnessing the PD-1 Pathway in Renal Cell Carcinoma: Current Evidence and Future Directions

Abhishek Tripathi,

Department of Internal Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Charles G. Drake, and

Department of Oncology and the Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA

Lauren C. Harshman

Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Lauren C. Harshman: laurenc_harshman@dfci.harvard.edu

Abstract

Programmed cell death-1 (PD-1) is a recognized immune checkpoint. It is frequently upregulated on the T cells that infiltrate tumors, providing an inhibitory signal, which may facilitate immune escape. Blocking antibodies have been developed to interrupt the interaction of PD-1 with its ligands PD-L1/PD-L2, with the goal of increasing the host antitumor immune response. Initial results have been encouraging, with durable responses in both treatment-naïve and pretreated patients, along with an acceptable toxicity profile. This tolerability makes PD-1 blockade an excellent potential partner for combination strategies with the approved targeted agents, such as tyrosine kinase inhibitors (TKIs) and anti-vascular endothelial growth factor (anti-VEGF) antibodies, as well as other investigational immune checkpoint inhibitors or agonist antibodies that may costimulate an immune response. PD-L1 expression on tumor cells and tumor-infiltrating immune cells is also being evaluated as a predictive biomarker of response to treatment. This review summarizes the biological basis, preclinical studies, ongoing trials, and future challenges associated with targeting the PD-1 pathway in renal cell carcinoma.

1 Introduction

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, with approximately 64,000 new cases and 14,000 deaths annually in the USA [1]. Clear cell renal cell carcinomas (ccRCC) are the most common pathological subtype (75–85 %), with papillary RCCs constituting the most frequent non-clear cell subtype and accounting for 10–15 % of cases [2, 3]. Approximately 25–30 % of cases present with locally advanced or metastatic disease at the time of diagnosis [4]. For patients with nonmetastatic disease, surgical resection with curative intent is the preferred modality of treatment. Metastatic

ccRCC is generally unresponsive to conventional chemotherapy agents. However, with the advent of targeted therapies that suppress angiogenesis, as well as agents that inhibit the mechanistic (formerly mammalian) target of rapamycin (mTOR) pathway, we have made great strides in the treatment of this disease [5–11]. Prior to the development of these targeted therapies, immunotherapy with interferon (IFN)- α and interleukin (IL)-2 based regimens were frequently utilized, but objective responses were generally observed in only 15–20 % of patients, with an unclear survival benefit. While associated with significant toxicity, high-dose IL-2 remains the only agent that can induce long-term remissions off therapy. However, this favorable result occurs in fewer than 10 % of patients [12–14]. While not completely understood, the mechanism of action of IL-2 is at least in part attributable to stimulation of antitumor immunity through stimulation of helper T cells and cytotoxic T lymphocytes (CTLs) [15]. Other immune stimulating strategies using adoptive T cell immunotherapies and vaccines have been attempted in RCC and have demonstrated evidence of immune responses but achieved only modest clinical effects [16–22].

Significant lymphocytic infiltrate has been observed in ccRCC specimens, suggesting an ongoing antitumor immune response [23]. However, these effector lymphocytes tend to be dysfunctional and incapable of eliminating tumor cells, implying that factors in the tumor microenvironment may facilitate host immune evasion by suppressing T cell activation and release of immune-stimulating cytokines [24]. The identification of large numbers of tumor-infiltrating lymphocytes (TILs) and the real, albeit modest, responses to cytokine-based immunotherapeutics, such as IFN- α and high-dose IL-2, suggest a role for harnessing the host antitumor immune response, and make the novel, somewhat more targeted immunotherapeutics, such as programmed cell death-1 (PD-1) pathway-blocking agents, attractive in RCC.

2 Biological Basis of Targeting the PD-1 Axis

First postulated in the early 1960s by Lewis Thomas and later embraced and magnified by Frank Macfarlane Burnet [25], the concept of cancer immunosurveillance is based on the premise that immune cells continuously screen host tissues for malignant cells on the basis of their expression of tumor-specific antigens and eliminate them before they become problematic [25–29]. Elimination of tumor cells occurs through a variety of mechanisms, including the tumoricidal effects of CD8+ CTLs [30–32] and natural killer (NK) cells [33]. These effector cells are supported by Th1+ CD4+ helper T cells [34], which can support CTL activation and expansion through the CD40/CD154 pathway [35] and secretion of IL-2, resulting in tumor antigen-specific CTL propagation [36]. Although initially controversial [37], mouse models demonstrating increased tumorigenesis in the absence of type 1 IFNs provided supportive evidence for this concept [38].

A more contemporary hypothesis by Schreiber et al. [39], known as “immunoediting” or the “three E’s,” details three phases of balance between the host immune system and tumors: elimination, equilibrium, and escape. The theory asserts that early tumors can be eliminated by the immune system before they become detectable. Later, tumor cells that escape the initial phase of elimination can persist at low levels and enter in to an equilibrium stage. In this phase, interactions between the immune system and tumor cells sculpt the subsequent

generation of cells, driving the evolution of less immunogenic tumor cells through multiple mechanisms. Data from mouse models support this theory. When tumor cells derived from immunodeficient mice were introduced into their syngeneic immunocompetent controls, they were unable to proliferate or induce new primaries [40]. It is postulated that the tumor cells originating in immunodeficient mice are more immunogenic than those that develop in their counterparts whose immune system remained intact and was likely able to eliminate the more immunogenic tumors. In contrast, when tumor cells from immunocompetent mice are transplanted into immunodeficient controls, they proliferate, theoretically because of diminished immunosurveillance and the lower immunogenicity of the tumor cells that survive a competent immune system [29, 40–44].

During this equilibrium phase, these inherently genetically unstable tumors can evolve to evade immune recognition and can secrete cytokines and express proteins that can induce immune suppression. These are the tumors that eventually progress to the stage known as “immune escape.” Possible mechanisms underlying this phenomenon include antigen loss, defects in antigen presentation (e.g., loss of MHC class I) [41], induction of central tolerance [45], induction of T cell anergy due to activation in the absence of appropriate costimulation [46], expression of inhibitory molecules, such as PD-L1 [47], and recruitment of regulatory T (Treg) cells [48].

Normal T cell activation requires the presentation of the MHC-antigen complex to the T cell receptor with costimulatory molecules CD28 on T cells and B7 on antigen-presenting cells, which leads to activation, clonal expansion, and differentiation of naive T cells into effector T cells [49]. However, the response is complex and is tightly regulated by co-inhibitory pathways, such as PD-1 and CTL-associated molecule-4 (CTLA-4), which has earned them their “immune checkpoint” moniker [49–51].

PD-1 is an inhibitory receptor expressed on CD4+ and CD8+ T cells, dendritic cells (DCs), B cells, and NK cells [52, 53]. Its expression can be induced by cytokines such as IL-2, IL-7, IL-15, and IL-21 [54]. PD-1 is intricately involved in maintenance of immune tolerance in peripheral tissues, as demonstrated by the development of autoimmune disorders in mice lacking PD-1 [55]. It has two known ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC). PD-L1 can be constitutively expressed on T lymphocytes, B cells, macrophages, myocytes, hepatocytes, and pancreatic beta cells. [53, 55–58]. Comparatively, PD-L2 expression is less ubiquitous and is mostly seen on mast cells and macrophages. PD-L1 expression is upregulated on tumor cells and TILs in a variety of solid tumors, including ccRCC, melanoma, non-small-cell lung cancer (NSCLC), urothelial cancers, ovarian cancer, and pancreatic carcinoma [59–64]. Higher expression has been associated with a higher tumor grade, poorer response to treatment, and higher mortality [65–71].

The PD-1/PD-L1 interaction inhibits T cell function through induction of apoptosis, inhibition of cytokine release, decreased T cell clonal expansion and, subsequently, an attenuated antitumor immune response [51, 55]. It also promotes the differentiation of CD4+/CD25–T lymphocytes into Tregs. These Tregs further suppress local antitumor immunity by inhibiting the function of antigen-presenting cells, secreting immunosuppressive cytokines, and suppressing effector cells [72]. The presence of Tregs in

tumors is often an independent poor prognostic factor [23]. Monoclonal antibodies designed to block the PD-1/PD ligand interaction can reverse immune evasion and have been shown in vitro to increase cell-mediated antitumor immunity in experimental models [73] (Fig. 1).

3 Characterization of Expression of PD-L1 in RCC

While normal renal tissue generally has no or only minimal PD-L1 expression, increased expression can be seen in inflammatory conditions of the kidney and RCC [69, 74]. Several groups have characterized PD-L1 expression in RCC and noted its association with prognosis (Table 1). One of the first studies evaluating PD-L1 expression in RCC analyzed 196 fresh frozen specimens by immunohistochemistry (IHC) using 5H1, an anti-PD-L1 monoclonal antibody [69]. PD-L1 expression was noted in 66 % of tumor cells and in 59 % of TILs. Similar rates of PD-L1 expression have been found in unmatched metastatic lesions [68]. High-level expression in tumor cells (10 %) or TILs (an adjusted lymphocyte score of >100, defined as moderate to marked lymphocytic infiltration with >50 % of the lymphocytes staining positive for B7-H1) was observed in 45 % of patients. With a median 2 years of follow-up after nephrectomy, patients whose tumors had a higher level of expression were more likely to have poor prognostic features such as a higher nuclear grade, to have lymph node or distant metastasis, and to succumb to recurrent cancer [68, 69]. As techniques for detection of PD-L1 in paraffin-embedded samples have become available, long-term retrospective follow-up of patients has become possible. In 2006, Thompson et al. [75] reported their 10-year follow up of 306 patients with ccRCC treated with nephrectomy between 1990 and 1994. Of the 306 patients, 24 % had high-level expression (defined as 10 %). Higher expression was associated with a two times higher risk of death (relative risk [RR] 2.00; 95 % confidence interval [CI] 1.27–3.15; $p = 0.003$) and decreased 5-year survival rates (41.9 versus 82.9 %). Furthermore, in patients with localized disease at the time of nephrectomy, PD-L1 positivity was found to be significantly associated with the risk of cancer progression (RR 3.46; 95 % CI 2.11–5.69; $p < 0.001$) [75]. PD-L1 expression was also evaluated in combination with levels of survivin, which inhibits apoptosis in tumor cells by inhibiting mitochondrial caspases. Patients with increased expression of both survivin and PD-L1 had significantly lower 5-year survival rates than patients with increased expression of only one marker or low expression [76]. Interestingly, this correlation between PD-L1 expression and poor outcomes may not be a universal finding among tumor types; Taube et al. [77] showed that higher PD-L1 expression was associated with increased T cell infiltration and improved outcomes in patients with melanoma.

Recognizing the intratumoral heterogeneity of RCC and the possibility of differences in protein expression between the primary tumor and metastases [78], McDermott and colleagues [79] evaluated whether PD-L1 expression in 34 nephrectomy samples correlated with their matched metastasis. PD-L1 positivity was defined as the presence of any tumor cells with membranous staining. Of the 34 primary RCC samples, 29 % were positive ($n = 10$). Seventy percent of these had matched positive metastasis ($n = 7$). In another study evaluating PD-L1 expression in matched specimens from primary and metastatic sites, Jilaveanu et al. [80] observed discordance between the two tissue types. Samples from metastatic sites showed significantly higher levels of expression than primary tumor samples. If the predictive capacity of PD-L1 expression bears out, the weak correlation ($R =$

0.24) suggests the need for independent analysis of the metastatic lesions in addition to the primary sample at the time of systemic therapy initiation or change, given the possibility of intratumoral heterogeneity or upregulation of PD-L1 expression in metastases that do not exist in the primary specimen.

4 PD-1 Pathway-Blocking Antibodies Under Clinical Development

4.1 Nivolumab

Nivolumab is a fully human IgG4 antibody, which binds to PD-1 and prevents its interaction with both PD-L1 and PD-L2. It was first evaluated in humans in a multicenter, open-label, phase 1 dose-escalation study in 39 patients with treatment-refractory metastatic melanoma, NSCLC, castrate-resistant prostate cancer (CRPC), RCC, or colorectal cancer (CRC) [81]. In that trial, patients were treated in dose-escalation arms between 0.3 and 10 mg/kg and an expansion group of 10 mg/kg. No dose-limiting toxicities (DLTs) were reported in the study. The most common adverse events (AEs) were decreased CD4+ lymphocyte counts (35.9 %), fatigue, and musculoskeletal events (15.4 %). Treatment-related immune-mediated AEs included inflammatory colitis and hypothyroidism in one patient each and polyarticular arthropathy in two patients. Toxicities were reversible with discontinuation of the antibody or treatment with steroids, thyroid supplementation, or immunosuppressants, such as infliximab. Two patients in this trial had long-term complete responses, one with RCC and one with CRC [82]. Despite the small sample size ($n = 9$), a modest correlation was seen between tumor PD-L1 expression and the likelihood of response ($p = 0.047$) [81].

In a larger phase 1 dose-escalation study, Topalian et al. [83] subsequently evaluated nivolumab in 296 patients with advanced melanoma, NSCLC, RCC, CRPC, or CRC. Patients were treated in dose-escalation cohorts of 1–10 mg/kg every 2 weeks. The treatment was well tolerated, with only 5 % of patients requiring treatment discontinuation because of intolerable AEs. The most common treatment-related AEs included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea, with 14 % of these events being grade 3 or 4. Immune-related AEs were seen in 41 % of patients ($n = 122$) and included pneumonitis, colitis, hepatitis, transaminitis, hypophysitis, and thyroid abnormalities; 6 % ($n = 18$) were grade 3 or higher. Treatment-related pneumonitis was seen in 3 % of patients ($n = 9$), with three cases being severe, such that they required mycophenolate mofetil (MMF), infliximab, or both, in addition to steroids. There were three treatment-related deaths due to pneumonitis, although none of these were RCC patients. Interestingly, the occurrence of pneumonitis did not correlate with the type of tumor, the presence of lung metastases, the dose, or the number of doses received.

Among the 34 patients with RCC, objective responses were achieved in 27 % of patients ($n = 9$). The duration of these responses ranged from 6 to 23 months, with several responses ongoing. Another 27 % ($n = 9$) experienced disease stabilization according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and 56 % of patients were progression free at 24 weeks. Of 42 patients with available biopsy samples, 25 were positive for PD-L1, with 36 % of these patients ($n = 9$) having objective responses. Of the five RCC samples, four were positive for PD-L1 expression, with objective responses in 50 % ($n = 2$),

including one complete response. The PD-L1-negative patient did not have evidence of an objective response.

On the basis of the initial responses observed in RCC, Motzer et al. [84] conducted a randomized, blinded, phase 2 trial to find the optimal dose of nivolumab on the basis of progression-free survival (PFS) [ClinicalTrials.gov identifier: NCT01354431]. A total of 168 RCC patients who had progressed on prior treatment with at least one antiangiogenic agent were randomized to receive nivolumab at 0.3, 2, and 10 mg/kg every 3 weeks until disease progression or intolerable toxicity occurred. The primary end point was to assess whether PFS with nivolumab was dose dependent. Interestingly, no significant dose–response relationship was observed ($p = 0.9$), with PFS ranging from 2.7 with the lowest dose to 4.2 months with the highest. Across all dose groups, objective responses were seen in 20–22 % of patients (Table 2). The median overall survival results were encouraging at approximately 2 years for the 2 and 10 mg/kg dose cohorts. The study also confirmed the safety profile observed in the phase 1 studies, as well as the overall tolerability of this agent, with only 6 % of patients discontinuing study therapy for drug-related toxicity. No grade 3 or 4 pneumonitis was reported.

A phase 1 biomarker study has also been completed, which recruited 67 patients with metastatic ccRCC. The treatment schema for this trial was identical to that used in the dose-finding study described above, with the goals of characterizing the immunomodulatory activity of the agent and identifying potential predictive biomarkers (Clinical-Trials.gov identifier: NCT01358721) [85]. Patients who had progressed on at least one antiangiogenic agent were randomized to receive one of three doses (0.3, 2, or 10 mg/kg) given every 3 weeks. A fourth arm enrolled treatment-naïve patients to receive the 10 mg/kg dose. Objective responses were achieved in 15 %, and the PFS rate at 24 weeks was 36 %. Assessment of the effect of nivolumab on serum chemokines was performed along with evaluation of tumor immune infiltrates and expression of PD-L1 before and after treatment with nivolumab. Certain chemokines were increased post-therapy, including the T cell chemoattractants chemokine (C-X-C motif) ligand (CXCL)-9 (90 %) and CXCL10 (30 %), which can be induced by IFN- γ . Increases in tumor-infiltrating CD3+ T cells (78 %) and CD8+ T cells (88 %) were also observed. Higher tumor PD-L1 expression correlated with a greater chance of response but did not guarantee response (22 versus 8 %).

Building on the established clinical benefit of tyrosine kinase inhibitors (TKIs) in RCC and the potential for synergy with another immune checkpoint inhibitor [87, 88], nivolumab is being evaluated in combination with pazopanib, sunitinib, or ipilimumab (ClinicalTrials.gov identifier: NCT01472081) [89, 90]. Patients with advanced or metastatic RCC were recruited in dose-escalation cohorts and received nivolumab at 2.0 and 5.0 mg/kg (the N2 and N5 dose cohorts) every 3 weeks, in combination with either sunitinib (S arm: 50 mg daily 4 weeks on, 2 weeks off) or pazopanib (P arm; 800 mg daily). A total of 33 patients were treated in the S arm, which included an expansion cohort of 19 patients at N5, while 20 patients were enrolled in the P arm at N2. Given four cases of DLTs in the P arm, including three due to liver toxicity, no dose escalation to the N5 dose occurred. It is important to note that the dose-escalation S arm cohort included primarily treatment-naïve patients ($N = 19$). While promising in terms of efficacy, the sunitinib–nivolumab combination did have a high

level of toxicity, with a higher rate of renal and liver AEs than expected. Up to 85 % of patients experienced a grade 3 or 4 AE, and 36 % of patients discontinued therapy because of drug-related toxicity. Overall, the most common treatment-related AEs included increased alanine transaminase (ALT), hypertension, and hyponatremia in the S arm and transaminitis and fatigue in the P arm. An objective response rate (ORR) of 52 % and 45 % were seen in the S and P arms, respectively and the responses tended to be durable (median duration of response: 37 and 31 weeks, respectively). Stable disease was the best response, observed in 30 and 35 % of patients in the S and P arms, respectively. When considering the 32–40 % of patients who had primary treatment-refractory disease in the phase 2 monotherapy trial, the low rate of primary refractory disease in the S arm was encouraging at 3 % ($n = 1$) and suggests the need to target multiple growth and resistance pathways. The median PFS was 49 weeks (~12 months, range 41.6–66 weeks) in the S arm and 31 weeks (~8 months, range 12.1–48.1 weeks) in the P arm. Although this trial is no longer recruiting patients to receive anti-PD-1 plus a TKI, an ongoing phase 2 trial is combining a different PD-1-blocking antibody pembrolizumab (MK-3475; Merck) with the TKI pazopanib (ClinicalTrials.gov identifier: NCT02014636).

In the same trial, two separate arms evaluated combined checkpoint inhibition with nivolumab and ipilimumab (ClinicalTrials.gov identifier: NCT01472081) [90]. In the induction phase, ipilimumab was given every 3 weeks for four doses, in combination with nivolumab. Two dosing regimens were tested with either nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3 + I1) or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1 + I3). In the subsequent maintenance phase, patients received nivolumab alone every 2 weeks until disease progression or toxicity occurred. Compared with the mostly treatment-naïve S + N5 cohort, approximately 80 % of these patients had treatment-refractory disease. Objective responses were observed in 43 % of the N3 + I1 arm and in 48 % of the N1 + I3 arm. The median duration of response was 31 weeks in the I1 arm and had not been reached in the I3 arm, with ongoing responses in ~80 % of patients in both arms at the time of presentation. Stable disease was the best response, seen in 24 % and 35 % of patients, with an overall clinical benefit rate of 67 % and 82 % in the N3 + I1 and N1 + I3 arms, respectively. The median PFS of around 9–10 months in either arm and the 24-week PFS rates of 64–65 % were encouraging, given the treatment-refractory nature of the population. It should be noted that a prior phase 2 study evaluating ipilimumab in treatment-refractory metastatic RCC patients had shown only a modest ORR of 13 % [91], suggesting that the combination had an additive effect compared with monotherapy of either agent alone.

However, the added efficacy achieved by the nivolumab plus ipilimumab combinations was accompanied by significant toxicity. Nearly 76 % of patients in the N3 + I1 arm and 100 % of patients in the N1 + I3 arm had a treatment-related AE. While they were reported to be manageable with established treatment algorithms, grade 3–4 AEs were seen in 29 % and 61 %, respectively, with the most frequent events being elevations in lipase and amylase, transaminitis, diarrhea, and colitis. In terms of treatment-related immune-related AEs, no high-grade pneumonitis was observed, but 26 % had liver toxicity and 17 % had a gastrointestinal disorder with the higher dose of ipilimumab. No treatment-related deaths occurred. Given the promising antitumor activity and acceptable and manageable toxicity at

the lower ipilimumab dose, a phase 3 study is being planned to evaluate the combination in treatment-naïve RCC patients.

A second-line, phase 3 potential registration study of nivolumab in metastatic RCC has recently completed recruitment (ClinicalTrials.gov identifier: NCT01668784). Over 800 patients with advanced or metastatic ccRCC who have received prior antiangiogenic therapy were randomized in a 2:1 fashion to receive either nivolumab 3 mg/kg every 2 weeks or the mTOR inhibitor everolimus at a dose of 10 mg daily until disease progression or intolerable toxicity occurred. The primary end point is overall survival, but PFS, ORR, duration of response, and safety are key secondary outcomes. Correlative studies will evaluate the predictive potential of baseline tumor PD-L1 expression.

4.2 MPDL3280A

MPDL3280A is a fully human IgG1 antibody against PD-L1, which prevents its binding to both PD-1 and B7-1 (CD80) but spares the PD-1/PD-L2 interaction. This antibody has been engineered to lack effector function, by modifying its fragment crystallizable (Fc) region to minimize antibody-dependent cell toxicity (ADCC) and complement-dependent cytotoxicity (CDC), thus preventing depletion of activated effector T cells in the tumor microenvironment. MPDL3280A is currently being evaluated in a phase 1, open-label, dose-escalation study (ClinicalTrials.gov identifier: NCT01375842) in patients with advanced solid tumors, including RCC and hematological malignancies. In that study, MPDL3280A is being administered every 3 weeks at doses of 3, 10, 15, and 20 mg/kg, depending on the cohort. The initial experience in 53 ccRCC patients indicated that the treatment was well tolerated and showed evidence of activity [92]. The incidence of grade 3–4 AEs was 43 %, with 13 % of the events being attributed to the drug. No grade 3–5 pneumonitis or treatment-related deaths were reported. Among the 39 patients evaluated for efficacy, responses were observed at all dose levels, with an overall 24-week PFS of 50 %. A correlation was observed between higher PD-L1 expression in the tumor-infiltrating immune cells and a greater chance of objective response (Table 3).

A recently initiated, multicenter, open-label phase 2 trial is investigating MPDL3280A as monotherapy or in combination with bevacizumab as compared with a control arm of standard-dose sunitinib in patients with treatment-naïve, locally advanced or metastatic RCC (ClinicalTrials.gov identifier: NCT01984242). Patients will receive MPDL3280A 1,200 mg intravenously every 3 weeks for up to 1 year. Bevacizumab will be dosed at 15 mg/kg intravenously every 3 weeks. Patients receiving MPDL3280A or sunitinib monotherapy can cross over to the combination arm after evidence of disease progression. PFS is the primary end point, while safety and the incidence of AEs are important secondary outcome measures.

4.3 Pembrolizumab (MK-3475, Lambrolizumab)

Pembrolizumab is a humanized, monoclonal IgG4 kappa anti-PD-1 antibody, which minimizes ADCC and CDC because of an optimized Fc region. It was first studied in advanced melanoma patients in a phase 1 study by Hamid et al. [93]. In the 135-patient trial, treatment-related AEs were reported in 79 % of patients, with 13 % being grade 3 or higher.

Not surprisingly, the cohort receiving the highest dose and most frequent dosing (10 mg/kg every 2 weeks) experienced the highest rate of AEs. Immune-related AEs included pneumonitis (4 %; none were grade 3 or higher), diarrhea (20 %; one case being grade 3), hypothyroidism (8 %), hyperthyroidism, and adrenal insufficiency. An ORR of 37 % was observed. The median PFS across all patients was 31 weeks, with longer PFS (61 weeks) observed in patients receiving the higher dose. As mentioned above, pembrolizumab is currently being investigated in RCC in a phase 1/2 trial in combination with pazopanib in treatment-naïve patients with metastatic ccRCC (ClinicalTrials.gov identifier: NCT02014636). Using a dose-escalation design, the first phase of the study will determine the recommended phase 2 dose (RP2D), while the phase 2 component will evaluate the clinical efficacy of the combination as compared with either agent as monotherapy, with a primary end point of PFS. Another trial is evaluating axitinib in combination with pembrolizumab to find the safest and maximally tolerated doses (ClinicalTrials.gov identifier: NCT02133742). Given the DLTs seen with the nivolumab–pazopanib combination, it will be important to see if additive hepatotoxicity is a class effect of combining PD-1 antibodies with TKIs, or whether that toxicity is restricted to nivolumab.

4.4 BMS 936559

Brahmer et al. [94] evaluated BMS 936559, a fully human PD-L1-specific IgG4 monoclonal antibody, in patients with advanced solid tumors, including RCC. Treatment was administered in dose-escalation cohorts of 0.3, 1, 3, and 10 mg/kg every 2 weeks. Treatment-related adverse reactions were reported in 61 % of patients. Immune-related AEs were seen in 39 % of patients ($n = 81$), with 5 % of events ($n = 10$) being grade 3 or higher. These included rash, hypothyroidism, hepatitis, sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis. Among RCC patients, 12 % had objective responses lasting for 4 and 17 months. An additional 41 % had stable disease at 24 weeks. Considering the relatively modest response rate compared with those of other agents, this agent is currently not the subject of ongoing studies in cancer.

4.5 Pidilizumab

Pidilizumab (CT-011) is a humanized IgG1 monoclonal anti-PD-1 antibody initially evaluated in hematological malignancies, with 38 % of patients experiencing clinical responses [95]. An ongoing phase 2 trial is testing it in combination with a DC vaccine in patients with metastatic RCC (ClinicalTrials.gov identifier: NCT01441765). Patients will receive four cycles of pidilizumab (3 mg/kg intravenously) alone or in combination with one dose of the DC vaccine on day 8 of each cycle. Safety and the response rate over 2 years will be the primary outcome measures, while immunological responses (defined as the peak response post-therapy and ongoing response at 3 and 6 months), the effect on circulating Tregs, and overall survival are secondary outcomes.

5 Other Agents

In addition to the agents discussed above, there are multiple other PD-1 pathway-blocking agents in development. These include MEDI-4736 and AMP-224. Medi-4736 is a fully human anti-PD-L1 IgG1 antibody with an optimized Fc domain, currently being evaluated in

a phase 1 study in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT01693562). AMP-224 is a novel type of PD-1 pathway inhibitor [96]. It is a recombinant fusion protein incorporating the extracellular domain of PD-L2 with the Fc domain of IgG1. It is thought to act through depletion of T cells expressing high levels of PD-1, with a resultant increase in functional T cells, thus improving antitumor immunity. A phase 1, open-label, two-stage, multicenter trial in patients with advanced metastatic solid tumors is ongoing (Clinical-Trials.gov identifier: NCT01352884). The initial dose-escalation stage was aimed at identifying the maximum tolerated dose (MTD), while the second stage is evaluating the safety, pharmacokinetics, and preliminary clinical activity. Post-treatment decreases in peripheral T cells with high levels of PD-1 expression confirmed the purported mechanism of action [96]. Further, patients who experienced partial responses, mixed responses, or stable disease exhibited evidence of an increased functional T cell response (increases in IFN- γ , tumor necrosis factor [TNF]- α , IL-2, CD4+, and CD8+ T cells). The treatment was well tolerated despite a high rate (69 %) of infusion reactions.

6 Predictive Value of PD-L1

The degree of PD-L1 expression on the tumor and immune cells in the microenvironment may reflect dependence of the tumor on this pathway. As such, PD-L1 expression on tumor cells, tumor-infiltrating cells, and surrounding microenvironment immune cells is currently being evaluated as a predictor of response. Multiple studies have evaluated its predictive capacity in patients treated with VEGF-targeted therapies or high-dose IL-2, as well as the more recent PD-1 pathway antibodies. With respect to VEGF-targeted therapy, PD-L1 expression was evaluated as a predictor of response in 453 patients with metastatic ccRCC undergoing treatment with sunitinib or pazopanib in the first-line setting in a phase 3 trial [97]. PD-L1 expression was quantified in the tumor cells, using a somewhat complicated H score ($3 \times$ percentage of strongly staining nuclei + $2 \times$ percentage of moderately staining nuclei + percentage of weakly staining nuclei), as well as in tumor-associated macrophages (TAMs). Any degree of PD-L1 expression was seen in 36 % of patients and was associated with increased infiltration with TAMs, compared with lower expression. Increased expression of PD-L1 (an H score >50) was associated with shorter overall survival [pazopanib high/low: 32 months versus 20 months; sunitinib high/low: 28 months versus 15 months ($p = 0.046$)].

Cytokine-based immunotherapies (e.g., IL-2) exert antitumor effects in part through recruitment of T cells in the tumor microenvironment [15]. In vitro exposure to IL-2 has been shown to upregulate PD-L1 expression [54]. In the SELECT trial (ClinicalTrials.gov identifier: NCT00554515), over 120 patients received high-dose IL-2. Tumor samples were available from 113 patients and were stained for PD-L1 expression. Objective responses were significantly greater in patients whose tumors had >5 % PD-L1 expression than in those with PD-L1-negative samples (50 versus 19 %, $p = 0.012$), suggesting that intratumoral PD-L1 expression may be a predictor of response to high-dose IL-2 [98]. Further studies are needed to validate these findings.

Whether tumor PD-L1 expression can predict response to PD-1 pathway antibodies is an area of intense study. As shown in prior phase 1 studies, patients whose tumors have higher

levels of PD-L1 expression appear to have a greater chance of responding to nivolumab, although it is not guaranteed [83]. Powderly et al. [99] presented data from an analysis of tumor samples, including RCC, from patients enrolled in a phase 1 trial with MPDL3280A, the IgG4 anti-PD-L1 antibody. The tumor samples were analyzed using IHC and a proprietary Genentech immunochip. In contrast to the prior reported studies with other antibodies, this study focused on PD-L1 expression of the tumor-infiltrating immune cells and observed that increased pretreatment baseline PD-L1 expression was associated with an enhanced clinical response to MPDL3280A. Furthermore, patients with evidence of a response to treatment showed an adaptive increase in tumor PD-L1 expression and a Th1-predominant cellular infiltrate.

In the first evaluation of nivolumab in combination with either pazopanib, sunitinib, or ipilimumab, tumoral PD-L1 expression did not appear to correlate with response [89]. With use of both 1 % and 5 % cutoff points for PD-L1 positivity, the ORRs were either similar or actually higher in PD-L1-negative patients than in their PD-L1-positive counterparts in the ipilimumab or TKI arms. A similar lack of correlation was seen in melanoma patients treated with the ipilimumab and nivolumab combination [87]. Possible reasons underlying these observations include the small sample size used for IHC analysis and use of different antibodies than those used in prior studies.

In summary, the use of PD-L1 expression as a predictive marker requires further investigation. Issues include the notion that PD-L1 expression is dynamic. The degree of expression may change as the tumor evolves or metastasizes, in response to IFN- γ production by nearby effector T cells, or as a consequence of treatment [54, 79]. This reaction has been termed “adaptive immune escape.” Further, the PD-L1 expression of older samples may not accurately reflect the status of the tumor at the time of treatment [100]. Ultimately, validation will be required, and studies are ongoing to determine the utility of this biomarker.

7 Future Directions

It is unlikely that anti-PD-1 or anti-PD-L1 monotherapy will control progressive disease in the majority of patients. As such, combination therapy with proven systemic agents, such as VEGF-targeted therapies or other novel immunotherapy approaches, are rational strategies. In addition to driving tumor angiogenesis, VEGF may exert immunomodulatory effects by inhibiting DC function and T cell activation and may contribute to immune escape [101]. Supporting this concept are observations that VEGF blockade abrogates the inhibition of DC function in tumor-bearing mice treated with anti-VEGF antibody, compared with controls [102]. Long-lasting decreases in tumor growth were observed when VEGF blockade was combined with DC immunotherapy and were associated with a pronounced antitumor CTL response in comparison with immunotherapy alone, thus indicating the immune-potentiating effects of VEGF blockade. Further, inhibitors of the VEGF pathway have been shown to decrease populations of immunosuppressive cells such as Tregs [103] and myeloid-derived suppressor cells (MDSCs) [104] in the tumor microenvironment. Similar immune-potentiating effects have been seen with other TKIs [103, 105]. The impact of VEGF inhibition on PD-L1 expression is an area of active investigation. Animal models suggest

that treatment with VEGF TKIs induces PD-L1 expression [Drake et al., unpublished data]. A conflicting report in humans who received sunitinib and pazopanib neoadjuvantly prior to nephrectomy showed a decrease in PD-L1 expression in nephrectomy specimens compared with the baseline biopsies ($p < 0.05$) [106]. A limitation of the neoadjuvant clinical trial results is that the biopsy may not accurately reflect the PD-L1 expression of the entire specimen. In contrast, the phase 1 VEGF receptor TKI/nivolumab combination data from Amin et al. [89] support the combined approach, given the high ORRs. Notably, there was a lack of correlation with baseline PD-L1 expression status in the combination study. However, toxicity may be a limiting factor with this approach. Multiple studies are ongoing or in development to further evaluate combined PD-1/VEGF blockade in RCC.

Exposure to IL-2 and IFN- γ can induce PD-L1 expression in tumors [54, 107], and high PD-L1 expression in tumors has been shown to correlate with increased response to high-dose IL-2 [98]. These observations suggest that combining PD-1-blocking agents with cytokine-based immunotherapy, such as IFN- α and IL-2, may enhance the antitumor immune response, as well as potentially broadening the patient population likely to benefit from PD-1 pathway inhibitors.

Combining PD-1 blockade with other immune checkpoint inhibitors, such as anti-CTLA-4, has been shown to enhance T cell activation and effector function in preclinical studies [88]. Significant synergy has been demonstrated with the combination of ipilimumab and nivolumab in advanced melanoma patients [87] and subsequently in RCC, although at the cost of higher toxicity in the group receiving higher doses of ipilimumab [90]. Randomized testing of this combination in RCC is planned.

Lymphocyte-activation gene 3 (LAG3) is another immune checkpoint receptor, co-expressed on TILs with PD-1. It promotes Treg development and decreases DC differentiation and function [108]. By synergizing with PD-1, LAG3 may diminish the antitumor immune response [108, 109]. Combined blockade of the PD-1 and LAG3 pathways induces tumor regression in murine melanoma models [110] and is currently being studied in a phase 1 trial in solid tumors (ClinicalTrials.gov identifier: NCT01968109).

Immune stimulation with DC/tumor fusion vaccines may upregulate PD-L1, which may lead to blunting of the antitumor immune response [111]. Combining PD-1 blockade with DC fusion vaccines has been shown to potentiate tumor cell killing in melanoma and myeloma patients [111], and one such combination with CT-011 and a DC/RCC fusion vaccine is being studied in a phase 2 trial in advanced RCC patients (ClinicalTrials.gov identifier: NCT01441765).

Lastly, killer cell immunoglobulin-like receptor (KIR) is an inhibitor of NK cell-mediated cytotoxicity, and anti-KIR agents have shown clinical activity in hematological malignancies [112]. Combined blockade of KIR and the PD-1 pathway represents another opportunity for sequential immune checkpoint blockade and is being tested in a phase 1 trial in patients with advanced solid tumors, including RCC (ClinicalTrials.gov identifier: NCT01714739).

8 Conclusions

RCC may evade the host immune system by exploiting the PD-1/PD-L1 pathway to its advantage. Blockade of the PD-1/PD-L1 interaction can overcome this immune evasion and increase antitumor immunity. Early-phase studies in patients with ccRCC and other solid tumors have revealed significant response rates, increased PFS, an acceptable toxicity profile, and encouraging overall survival results. Higher PD-L1 expression on tumors and tumor-infiltrating cells appears to enrich the response, but use of PD-L1 expression as a predictive biomarker requires further validation. Combinations of PD-1 pathway inhibitors with other immune modulators or targeted therapies are under evaluation. Their synergy could be key to improving outcomes in advanced RCC.

Acknowledgments

Abhishek Tripathi has no conflicts of interest to report.

Charles G. Drake has received research funding from Bristol-Myers Squibb (BMS), Advro Biotech, and Janssen Pharmaceuticals; participated in advisory boards for BMS, Compugen, Dendreon, Immun-Excite, Roche/Genentech, and Pfizer; received manuscript preparation support from BMS (not for this work); received stock options from Comugen; and received royalties from Amplimmune.

Lauren C. Harshman has received past research funding from BMS; receives current research funding from Pfizer and Astellas/Medivation; and has participated in advisory boards for BMS, Pfizer, NCCN, Dendreon, and Aveo.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014; 64(1):9–29. DOI: 10.3322/caac.21208 [PubMed: 24399786]
2. Storkel S, van den Berg E. Morphological classification of renal cancer. *World J Urol.* 1995; 13(3): 153–8. [PubMed: 7550386]
3. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman A, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol.* 2005; 23(12): 2763–71. DOI: 10.1200/JCO.2005.07.055 [PubMed: 15837991]
4. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med.* 1996; 335(12):865–75. DOI: 10.1056/NEJM199609193351207 [PubMed: 8778606]
5. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007; 356(22):2271–81. DOI: 10.1056/NEJMoa066838 [PubMed: 17538086]
6. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet.* 2007; 370(9605):2103–11. DOI: 10.1016/S0140-6736(07)61904-7 [PubMed: 18156031]
7. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol.* 2008; 26(33):5422–8. DOI: 10.1200/JCO.2008.16.9847 [PubMed: 18936475]
8. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007; 356(2):115–24. DOI: 10.1056/NEJMoa065044 [PubMed: 17215529]
9. Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVO-REN): final analysis of overall survival. *J Clin Oncol.* 2010; 28(13):2144–50. DOI: 10.1200/JCO.2009.26.7849 [PubMed: 20368553]

10. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III Treatment Approaches in Renal Cancer Global Evaluation trial. *J Clin Oncol*. 2009; 27(20):3312–8. DOI: 10.1200/JCO.2008.19.5511 [PubMed: 19451442]
11. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer*. 2010; 116(18):4256–65. DOI: 10.1002/cncr.25219 [PubMed: 20549832]
12. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartz-entruber DJ, Hwu P, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol*. 2003; 21(16):3127–32. DOI: 10.1200/JCO.2003.02.122 [PubMed: 12915604]
13. McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2005; 23(1):133–41. DOI: 10.1200/JCO.2005.03.206 [PubMed: 15625368]
14. Klapper JA, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma: a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. *Cancer*. 2008; 113(2):293–301. DOI: 10.1002/cncr.23552 [PubMed: 18457330]
15. Rosenberg SA, Mule JJ, Spiess PJ, Reichert CM, Schwarz SL. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2. *J Exp Med*. 1985; 161(5):1169–88. [PubMed: 3886826]
16. Graham S, Babayan RK, Lamm DL, Sawczuk I, Ross SD, Lavin PT, et al. The use of ex vivo-activated memory T cells (autolymphocyte therapy) in the treatment of metastatic renal cell carcinoma: final results from a randomized, controlled, multisite study. *Semin Urol*. 1993; 11(1):27–34. [PubMed: 8465126]
17. Kugler A, Stuhler G, Walden P, Zoller G, Zobywalski A, Brossart P, et al. Regression of human metastatic renal cell carcinoma after vaccination with tumor cell-dendritic cell hybrids. *Nat Med*. 2000; 6(3):332–6. DOI: 10.1038/73193 [PubMed: 10700237]
18. Holtl L, Zelle-Rieser C, Gander H, Papesh C, Ramoner R, Bartsch G, et al. Immunotherapy of metastatic renal cell carcinoma with tumor lysate-pulsed autologous dendritic cells. *Clin Cancer Res*. 2002; 8(11):3369–76. [PubMed: 12429623]
19. Florcken A, Kopp J, van Lessen A, Movassaghi K, Takvorian A, Johrens K, et al. Allogeneic partially HLA-matched dendritic cells pulsed with autologous tumor cell lysate as a vaccine in metastatic renal cell cancer: a clinical phase I/II study. *Hum Vaccines Immunother*. 2013; 9(6):1217–27. DOI: 10.4161/hv.24149
20. Rosenberg SA, Lotze MT, Yang JC, Topalian SL, Chang AE, Schwartzentruber DJ, et al. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst*. 1993; 85(8):622–32. [PubMed: 8468720]
21. Tomita Y, Katagiri A, Saito K, Imai T, Saito T, Tanikawa T, et al. Adoptive immunotherapy of patients with metastatic renal cell cancer using lymphokine-activated killer cells, interleukin-2 and cyclophosphamide: long-term results. *Int J Urol*. 1998; 5(1):16–21. [PubMed: 9535595]
22. May M, Brookman-May S, Hoschke B, Gilfrich C, Kendel F, Baxmann S, et al. Ten-year survival analysis for renal carcinoma patients treated with an autologous tumour lysate vaccine in an adjuvant setting. *Cancer Immunol Immunother*. 2010; 59(5):687–95. DOI: 10.1007/s00262-009-0784-6 [PubMed: 19876628]
23. Kang MJ, Kim KM, Bae JS, Park HS, Lee H, Chung MJ, et al. Tumor-infiltrating PD1-positive lymphocytes and FoxP3-positive regulatory T cells predict distant metastatic relapse and survival of clear cell renal cell carcinoma. *Transl Oncol*. 2013; 6(3):282–9. [PubMed: 23730407]
24. Frankenberger B, Noessner E, Schendel DJ. Immune suppression in renal cell carcinoma. *Semin Cancer Biol*. 2007; 17(4):330–43. DOI: 10.1016/j.semcancer.2007.06.004 [PubMed: 17656104]
25. Parish CR. Cancer immunotherapy: the past, the present and the future. *Immunol Cell Biol*. 2003; 81(2):106–13. DOI: 10.1046/j.0818-9641.2003.01151.x [PubMed: 12631233]

26. Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Investig.* 2007; 117(5):1137–46. DOI: 10.1172/JCI31405 [PubMed: 17476343]
27. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity.* 2004; 21(2):137–48. DOI: 10.1016/j.immuni.2004.07.017 [PubMed: 15308095]
28. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol.* 2004; 22:329–60. DOI: 10.1146/annurev.immunol.22.012703.104803 [PubMed: 15032581]
29. Burnet FM. Immunological surveillance in neoplasia. *Transplant Rev.* 1971; 7:3–25. [PubMed: 5146537]
30. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. *Immunology.* 2007; 121(1):1–14. DOI: 10.1111/j.1365-2567.2007.02587.x [PubMed: 17386080]
31. Tanaka H, Yoshizawa H, Yamaguchi Y, Ito K, Kagamu H, Suzuki E, et al. Successful adoptive immunotherapy of murine poorly immunogenic tumor with specific effector cells generated from gene-modified tumor-primed lymph node cells. *J Immunol.* 1999; 162(6):3574–82. [PubMed: 10092816]
32. Maher J, Davies ET. Targeting cytotoxic T lymphocytes for cancer immunotherapy. *Br J Cancer.* 2004; 91(5):817–21. DOI: 10.1038/sj.bjc.6602022 [PubMed: 15266309]
33. Terabe M, Berzofsky JA. The role of NKT cells in tumor immunity. *Adv cancer Res.* 2008; 101:277–348. DOI: 10.1016/S0065-230X(08)00408-9 [PubMed: 19055947]
34. Keene JA, Forman J. Helper activity is required for the in vivo generation of cytotoxic T lymphocytes. *J Exp Med.* 1982; 155(3):768–82. [PubMed: 6801178]
35. Mackey MF, Barth RJ Jr, Noelle RJ. The role of CD40/CD154 interactions in the priming, differentiation, and effector function of helper and cytotoxic T cells. *J Leukoc Biol.* 1998; 63(4):418–28. [PubMed: 9544571]
36. Smith KA. Interleukin-2: inception, impact, and implications. *Science.* 1988; 240(4856):1169–76. [PubMed: 3131876]
37. Stutman O. Tumor development after 3-methylcholanthrene in immunologically deficient athymic-nude mice. *Science.* 1974; 183(4124):534–6. [PubMed: 4588620]
38. Kaplan DH, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, et al. Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. *Proc Natl Acad Sci.* 1998; 95(13):7556–61. [PubMed: 9636188]
39. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science.* 2011; 331(6024):1565–70. DOI: 10.1126/science.1203486 [PubMed: 21436444]
40. Teng MW, Swann JB, Koebel CM, Schreiber RD, Smyth MJ. Immune-mediated dormancy: an equilibrium with cancer. *J Leukoc Biol.* 2008; 84(4):988–93. DOI: 10.1189/jlb.1107774 [PubMed: 18515327]
41. Seliger B, Maeurer MJ, Ferrone S. Antigen-processing machinery breakdown and tumor growth. *Immunol Today.* 2000; 21(9):455–64. [PubMed: 10953098]
42. Algarra I, Cabrera T, Garrido F. The HLA crossroad in tumor immunology. *Hum Immunol.* 2000; 61(1):65–73. [PubMed: 10658979]
43. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. *Adv Immunol.* 2006; 90:1–50. DOI: 10.1016/S0065-2776(06)90001-7 [PubMed: 16730260]
44. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011; 144(5):646–74. DOI: 10.1016/j.cell.2011.02.013 [PubMed: 21376230]
45. Kyewski B, Klein L. A central role for central tolerance. *Annu Rev Immunol.* 2006; 24:571–606. DOI: 10.1146/annurev.immunol.23.021704.115601 [PubMed: 16551260]
46. Schwartz RH. T cell anergy. *Annu Rev Immunol.* 2003; 21:305–34. DOI: 10.1146/annurev.immunol.21.120601.141110 [PubMed: 12471050]
47. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med.* 2002; 8(8):793–800. DOI: 10.1038/nm730 [PubMed: 12091876]

48. Terabe M, Berzofsky JA. Immunoregulatory T cells in tumor immunity. *Curr Opin Immunol.* 2004; 16(2):157–62. DOI: 10.1016/j.coi.2004.01.010 [PubMed: 15023407]
49. Vigano S, Perreau M, Pantaleo G, Harari A. Positive and negative regulation of cellular immune responses in physiologic conditions and diseases. *Clin Dev Immunol.* 2012; 2012:485781.doi: 10.1155/2012/485781 [PubMed: 22548114]
50. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev.* 2010; 236:219–42. DOI: 10.1111/j.1600-065X.2010.00923.x [PubMed: 20636820]
51. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med.* 2000; 192(7):1027–34. [PubMed: 11015443]
52. Liang SC, Latchman YE, Buhlmann JE, Tomczak MF, Horwitz BH, Freeman GJ, et al. Regulation of PD-1, PD-L1, and PD-L2 expression during normal and autoimmune responses. *Eur J Immunol.* 2003; 33(10):2706–16. DOI: 10.1002/eji.200324228 [PubMed: 14515254]
53. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008; 26:677–704. DOI: 10.1146/annurev.immunol.26.021607.090331 [PubMed: 18173375]
54. Kinter AL, Godbout EJ, McNally JP, Sereti I, Roby GA, O'Shea MA, et al. The common gamma-chain cytokines IL-2, IL-7, IL-15, and IL-21 induce the expression of programmed death-1 and its ligands. *J Immunol.* 2008; 181(10):6738–46. [PubMed: 18981091]
55. Okazaki T, Honjo T. The PD-1–PD-L pathway in immunological tolerance. *Trends Immunol.* 2006; 27(4):195–201. DOI: 10.1016/j.it.2006.02.001 [PubMed: 16500147]
56. Cao J, Liu FX, Yu MX. Expression of programmed death 1 and its ligands in the liver of autoimmune hepatitis C57BL/6 mice. *Chin Med J.* 2009; 122(16):1941–6. [PubMed: 19781375]
57. Iwai Y, Terawaki S, Ikegawa M, Okazaki T, Honjo T. PD-1 inhibits antiviral immunity at the effector phase in the liver. *J Exp Med.* 2003; 198(1):39–50. DOI: 10.1084/jem.20022235 [PubMed: 12847136]
58. Wiendl H, Mitsdoerffer M, Schneider D, Chen L, Lochmuller H, Melms A, et al. Human muscle cells express a B7-related molecule, B7-H1, with strong negative immune regulatory potential: a novel mechanism of counterbalancing the immune attack in idiopathic inflammatory myopathies. *FASEB J.* 2003; 17(13):1892–4. DOI: 10.1096/fj.03-0039fje [PubMed: 12923066]
59. Huang DS, Liu JW, Geng L, Jiang GP, Shen GL, Yao WF. Role of B7-H1 in pancreatic carcinoma immune evasion. *Zhonghua Wai Ke Za Zhi.* 2009; 47(4):282–5. [PubMed: 19570392]
60. Atefi MS, Avramis E, Lassen A, Wong DJ, Robert L, Foulad D, et al. Effects of MAPK and PI3K pathways on PD-L1 expression in melanoma. *Clin Cancer Res.* 2014; doi: 10.1158/1078-0432.CCR-13-2797
61. Chavan R, Salvador D, Gustafson MP, Dietz AB, Nevala W, Markovic SN. Untreated stage IV melanoma patients exhibit abnormal monocyte phenotypes and decreased functional capacity. *Cancer Immunol Res.* 2014; 2(3):241–8. DOI: 10.1158/2326-6066.CIR-13-0094 [PubMed: 24778320]
62. Velcheti V, Schalper KA, Carvajal DE, Anagnostou VK, Syrigos KN, Sznol M, et al. Programmed death ligand-1 expression in non-small cell lung cancer. *Lab Invest.* 2014; 94(1):107–16. DOI: 10.1038/labinvest.2013.130 [PubMed: 24217091]
63. Boorjian SA, Sheinin Y, Crispen PL, Farmer SA, Lohse CM, Kuntz SM, et al. T-cell coregulatory molecule expression in urothelial cell carcinoma: clinicopathologic correlations and association with survival. *Clin Cancer Res.* 2008; 14(15):4800–8. DOI: 10.1158/1078-0432.CCR-08-0731 [PubMed: 18676751]
64. Maine CJ, Aziz NH, Chatterjee J, Hayford C, Brewig N, Whilding L, et al. Programmed death ligand-1 over-expression correlates with malignancy and contributes to immune regulation in ovarian cancer. *Cancer Immunol Immunother.* 2014; 63(3):215–24. DOI: 10.1007/s00262-013-1503-x [PubMed: 24297569]
65. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci.* 2007; 104(9):3360–5. DOI: 10.1073/pnas.0611533104 [PubMed: 17360651]

66. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer*. 2007; 109(8):1499–505. DOI: 10.1002/cncr.22588 [PubMed: 17340590]
67. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother*. 2007; 56(8):1173–82. DOI: 10.1007/s00262-006-0266-z [PubMed: 17186290]
68. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer*. 2005; 104(10):2084–91. DOI: 10.1002/cncr.21470 [PubMed: 16208700]
69. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma patients: indicator of tumor aggressiveness and potential therapeutic target. *Proc Natl Acad Sci*. 2004; 101(49):17174–9. DOI: 10.1073/pnas.0406351101 [PubMed: 15569934]
70. Chen XL, Yuan SX, Chen C, Mao YX, Xu G, Wang XY. Expression of B7-H1 protein in human pancreatic carcinoma tissues and its clinical significance. *Ai Zheng*. 2009; 28(12):1328–32. [PubMed: 19958630]
71. Geng L, Huang D, Liu J, Qian Y, Deng J, Li D, et al. B7-H1 up-regulated expression in human pancreatic carcinoma tissue associates with tumor progression. *J Cancer Res Clin Oncol*. 2008; 134(9):1021–7. DOI: 10.1007/s00432-008-0364-8 [PubMed: 18347814]
72. Schmidt A, Oberle N, Krammer PH. Molecular mechanisms of Treg-mediated T cell suppression. *Front Immunol*. 2012; 3:51.doi: 10.3389/fimmu.2012.00051 [PubMed: 22566933]
73. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*. 2005; 65(3):1089–96. [PubMed: 15705911]
74. Ding H, Wu X, Gao W. PD-L1 is expressed by human renal tubular epithelial cells and suppresses T cell cytokine synthesis. *Clin Immunol*. 2005; 115(2):184–91. DOI: 10.1016/j.clim.2005.01.005 [PubMed: 15885642]
75. Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res*. 2006; 66(7):3381–5. DOI: 10.1158/0008-5472.CAN-05-4303 [PubMed: 16585157]
76. Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and b7-h1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. *Clin Cancer Res*. 2007; 13(6):1749–56. DOI: 10.1158/1078-0432.CCR-06-2129 [PubMed: 17363528]
77. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med*. 2012; 4(127):127ra37.doi: 10.1126/scitranslmed.3003689
78. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. 2012; 366(10):883–92. DOI: 10.1056/NEJMoa1113205 [PubMed: 22397650]
79. Callea M, Genega EM, Gupta M, Fay AP, Song J, Carvo I, et al. PD-L1 expression in primary clear cell renal cell carcinomas (ccRCCs) and their metastases. *ASCO Meeting Abstracts*. 2014; 32(4 Suppl):467.
80. Jilaveanu LB, Shuch B, Zito CR, Parisi F, Barr M, Kluger Y, et al. PD-L1 expression in clear cell renal cell carcinoma: an analysis of nephrectomy and sites of metastases. *J Cancer*. 2014; 5(3):166–72. DOI: 10.7150/jca.8167 [PubMed: 24563671]
81. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, 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. *J Clin Oncol*. 2010; 28(19):3167–75. DOI: 10.1200/JCO.2009.26.7609 [PubMed: 20516446]

82. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. *Clin Cancer Res.* 2013; 19(2):462–8. DOI: 10.1158/1078-0432.CCR-12-2625 [PubMed: 23169436]
83. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012; 366(26): 2443–54. DOI: 10.1056/NEJMoa1200690 [PubMed: 22658127]
84. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel T, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma (mRCC): results of a randomized, dose-ranging phase II trial. *ASCO Meeting Abstracts.* 2014; 32(15 Suppl):5009.
85. Choueiri TK, Fishman MN, Escudier BJ, Kim JJ, Kluger HM, Stadler WM, et al. Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma (mRCC): biomarker-based results from a randomized clinical trial. *ASCO Meeting Abstracts.* 2014; 32(15 Suppl):5012.
86. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol.* 2013; 14(6):552–62. DOI: 10.1016/S1470-2045(13)70093-7 [PubMed: 23598172]
87. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013; 369(2):122–33. DOI: 10.1056/NEJMoa1302369 [PubMed: 23724867]
88. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci.* 2010; 107(9):4275–80. DOI: 10.1073/pnas.0915174107 [PubMed: 20160101]
89. Amin A, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, 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). *ASCO Meeting Abstracts.* 2014; 32(15 Suppl):5010.
90. Hammers HJ, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF, et al. Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). *ASCO Meeting Abstracts.* 2014; 32(15 Suppl):4504.
91. Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, Topalian SL, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J Immunother.* 2007; 30(8):825–30. DOI: 10.1097/CJI.0b013e318156e47e [PubMed: 18049334]
92. Cho DC, Sosman JA, Sznol M, Gordon MS, Hollebecque A, Hamid O, et al. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with metastatic renal cell carcinoma (mRCC). *ASCO Meeting Abstracts.* 2013; 31(15 Suppl):4505.
93. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med.* 2013; 369(2):134–44. DOI: 10.1056/NEJMoa1305133 [PubMed: 23724846]
94. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012; 366(26):2455–65. DOI: 10.1056/NEJMoa1200694 [PubMed: 22658128]
95. Berger R, Rotem-Yehudar R, Slama G, Landes S, Kneller A, Leiba M, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin Cancer Res.* 2008; 14(10):3044–51. DOI: 10.1158/1078-0432.CCR-07-4079 [PubMed: 18483370]
96. Infante JR, Powderly JD, Burris HA, Kittaneh M, Grice JH, Smothers JF, et al. Clinical and pharmacodynamic (PD) results of a phase I trial with AMP-224 (B7-DC Fc) that binds to the PD-1 receptor. *ASCO Meeting Abstracts.* 2013; 31(15 Suppl):3044.
97. Choueiri TK, Figueroa DJ, Liu Y, Gagnon RC, Deen KC, Carpenter C, et al. Correlation of PDL1 tumor expression and treatment outcomes in patients with renal cell carcinoma (RCC) receiving tyrosine kinase inhibitors: COMPARZ study analysis. *ASCO Meeting Abstracts.* 2014; 32(4 Suppl):416.

98. Bailey AS, Cheng S, Kwon ED, Leibovich BC, Signoretti S, Dutcher JP, et al. Pdl-1/pdl-3 (programmed death ligand-1/3) tissue expression and response to treatment with IL2 and anti-angiogenic therapies. ASCO Meeting Abstracts. 2013; 31(15 Suppl):4521.
99. Powderly JD, Koeppen H, Hodi FS, Sosman JA, Gettinger SN, Desai R, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. ASCO Meeting Abstracts. 2013; 31(15 Suppl):3001.
100. Di Napoli A, Signoretti S. Tissue biomarkers in renal cell carcinoma: issues and solutions. Cancer. 2009; 115(10 Suppl):2290–7. DOI: 10.1002/cncr.24233 [PubMed: 19402057]
101. Laxmanan S, Robertson SW, Wang E, Lau JS, Briscoe DM, Mukhopadhyay D. Vascular endothelial growth factor impairs the functional ability of dendritic cells through Id pathways. Biochem Biophys Res Commun. 2005; 334(1):193–8. DOI: 10.1016/j.bbrc.2005.06.065 [PubMed: 16002046]
102. Gabrilovich DI, Ishida T, Nadaf S, Ohm JE, Carbone DP. Antibodies to vascular endothelial growth factor enhance the efficacy of cancer immunotherapy by improving endogenous dendritic cell function. Clin Cancer Res. 1999; 5(10):2963–70. [PubMed: 10537366]
103. Takeuchi A, Eto M, Shiota M, Tatsugami K, Yokomizo A, Kuroiwa K, et al. Sunitinib enhances antitumor effects against chemotherapy-resistant bladder cancer through suppression of ERK1/2 phosphorylation. Int J Oncol. 2012; 40(5):1691–6. DOI: 10.3892/ijo.2012.1368 [PubMed: 22344606]
104. Ko JS, Zea AH, Rini BI, Ireland JL, Elson P, Cohen P, et al. Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients. Clin Cancer Res. 2009; 15(6):2148–57. DOI: 10.1158/1078-0432.CCR-08-1332 [PubMed: 19276286]
105. Seliger B, Massa C, Rini B, Ko J, Finke J. Antitumour and immune-adjuvant activities of protein-tyrosine kinase inhibitors. Trends Mol Med. 2010; 16(4):184–92. DOI: 10.1016/j.molmed.2010.02.001 [PubMed: 20304705]
106. Sharpe K, Stewart GD, Mackay A, Van Neste C, Roife C, Berney D, et al. The effect of VEGF-targeted therapy on biomarker expression in sequential tissue from patients with metastatic clear cell renal cancer. Clin Cancer Res. 2013; 19(24):6924–34. DOI: 10.1158/1078-0432.CCR-13-1631 [PubMed: 24130073]
107. Chen J, Feng Y, Lu L, Wang H, Dai L, Li Y, et al. Interferon-gamma-induced PD-L1 surface expression on human oral squamous carcinoma via PKD2 signal pathway. Immunobiology. 2012; 217(4):385–93. DOI: 10.1016/j.imbio.2011.10.016 [PubMed: 22204817]
108. Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res. 2012; 72(4):917–27. DOI: 10.1158/0008-5472.CAN-11-1620 [PubMed: 22186141]
109. Matsuzaki J, Gnjjatic S, Mhawech-Fauceglia P, Beck A, Miller A, Tsuji T, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. Proc Natl Acad Sci. 2010; 107(17):7875–80. DOI: 10.1073/pnas.1003345107 [PubMed: 20385810]
110. Goding SR, Wilson KA, Xie Y, Harris KM, Baxi A, Akpinarli A, et al. Restoring immune function of tumor-specific CD4+ T cells during recurrence of melanoma. J Immunol. 2013; 190(9):4899–909. DOI: 10.4049/jimmunol.1300271 [PubMed: 23536636]
111. Rosenblatt J, Glotzbecker B, Mills H, Vasir B, Tzachanis D, Levine JD, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother. 2011; 34(5):409–18. DOI: 10.1097/CJI.0b013e31821ca6ce [PubMed: 21577144]
112. Benson DM Jr, Hofmeister CC, Padmanabhan S, Suvannasankha A, Jagannath S, Abonour R, et al. A phase 1 trial of the anti-KIR antibody IPH2101 in patients with relapsed/refractory multiple myeloma. Blood. 2012; 120(22):4324–33. DOI: 10.1182/blood-2012-06-438028 [PubMed: 23033266]

Key Points

The programmed cell death-1 (PD-1) pathway may play an important role in immune evasion in renal cell carcinoma (RCC). PD-L1 is an inhibitory ligand frequently upregulated in RCC and is associated with worse prognosis.

Several blocking antibodies against the PD-1 receptor or PD-L1 are under investigation in RCC and have shown encouraging preliminary efficacy.

Further studies are needed to evaluate PD-L1 expression on tumor cells and tumor-infiltrating immune cells as a predictor of response with these agents.

Fig. 1. Role of programmed cell death-1 (PD-1) pathway in cell-mediated tumor cell death. *IFN* interferon, *MHC* major histocompatibility complex, *PD-L1* programmed cell death ligand-1, *TCR* T cell receptor

Table 1
Selected studies evaluating programmed cell death ligand-1 (PD-L1) expression in renal cell carcinoma (RCC)

Reference	n	Type of specimen	Median follow-up	PD-L1 positivity in tumor cells	Results/higher PD-L1 expression associated with:
Thompson et al. [69]	196	Fresh frozen ccRCC nephrectomy samples	2 years	66 % in tumor cells; 59 % in TILs	Increased mortality (RR 4.53; 95 % CI 1.94–10.56; $p < 0.001$) Increased regional lymph node involvement ($p < 0.001$) Distant metastases ($p = 0.02$) Advanced nuclear grade ($p < 0.001$) Adverse pathological features Advanced stage, tumor size > 5 cm, higher grade ($p < 0.001$) Increased risk of death (RR 2.00; 95 % CI 1.27–3.15; $p = 0.003$) Increased risk of cancer progression (RR 3.46; 95 % CI 2.11–5.69; $p < 0.001$) Increased TAMs Shorter OS ($p = 0.046$)
Thompson et al. [75]	306	Paraffin-embedded ccRCC nephrectomy samples	11 years	24 %	PD-L1+ associated with higher ORR (50 versus 19 %; $p = 0.012$)
Choueiri et al. [97]	453	Paraffin-embedded nephrectomy samples; patients later treated with VEGF-targeted therapy	NA	36 %	Higher PD-L1 expression in metastatic versus primary tumors ($p < 0.05$) Weak correlation between PD-L1 expression in primary and metastatic sites ($R = 0.24$)
Bailey et al. [98]	113	Paraffin-embedded nephrectomy samples; patients later treated with high-dose IL-2	NA	16 %	
Jilaveanu et al. [80]	34	Paraffin-embedded matched primary and metastatic ccRCC samples	NA	AQUA scores: primary: 15.5 %; metastases: 21.9 %	

AQUA automated quantitative analysis, ccRCC clear cell renal cell carcinoma, CI confidence interval, IL interleukin, NA not available, ORR objective response rate, OS overall survival, RR relative risk, TAMs tumor-associated macrophages, TILs tumor-infiltrating lymphocytes, VEGF vascular endothelial growth factor

Table 2

Summary of resulted trials evaluating anti-programmed cell death-1 (anti-PD-1) pathway agents in renal cell carcinoma (RCC)

Drug	Trial ^a	Phase	n	ORR	PFS ^b	OS
Nivolumab	Motzer et al. [84]; NCT01354431	2	168	20–22 %	0.3 mg/kg; 2.7 months 2 mg/kg; 4.0 months 10 mg/kg; 4.2 months ($p = 0.9$)	18 months 25 months 25 months
Nivolumab biomarker	Choueiri et al. [84]; NCT01358721	1	91	17 %	36 % at 24 weeks	NR
Nivolumab + ipilimumab	Hammers et al. [90]; NCT01472081	1	44	43 %	N3 + I1: 37 weeks N1 + I3: 38 weeks	NR
Nivolumab + sunitinib/pazopanib	Amin et al. [89]; NCT01472081	1	53	52 %	S + N: 49 weeks	NR
				45 %	P + N: 31 weeks	

NR not reported, ORR objective response rate, OS overall survival, PFS progression-free survival

^aThe NCT numbers are ClinicalTrials.gov identifiers

^bN3 + I1: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 21 days; N1 + I3: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 21 days; S + N: sunitinib + nivolumab; P + N: pazopanib + nivolumab

Table 3

Summary of completed and ongoing clinical trials evaluating programmed cell death-1 (PD-1)-blocking agents in advanced renal cell carcinoma (RCC)

Drug	Trial ^a	Phase	Treatment	Patients	Primary end point	Secondary end points
Nivolumab	Brahmer et al. [94]; NCT00730639	1	Nivolumab	Advanced solid tumors	Safety, tolerability	Pharmacokinetics, efficacy, immunogenicity
	Choueiri et al. [85]; NCT01358721	1 (biomarkers)	Nivolumab	Metastatic ccRCC with prior antiangiogenic therapy	Immunomodulatory activity	Safety, ORR, PFS
	Motzer et al. [84]; NCT01354431	2 (dose-ranging)	Nivolumab	Metastatic ccRCC with prior antiangiogenic therapy	PFS	ORR, OS
	NCT01668784 Registration trial	3	Nivolumab versus everolimus	Metastatic ccRCC with prior antiangiogenic therapy	OS (maturing)	PFS
MPDL3280A	Amin et al. [89]; Hammers et al. [90]; NCT01472081	1	Nivolumab with sunitinib, pazopanib, or ipilimumab	Metastatic RCC treated with IFN- α or IL-2	Safety, tolerability	ORR, duration of response
	NCT01714739	1	Nivolumab + lirilumab	Advanced solid tumors	Safety	ORR, PFS, pharmacokinetics
	NCT01375842	1	MPDL3280A	Metastatic or advanced solid tumors or hematologic malignancies	DLT	AEs
	NCT01984242	2	MPDL3280A versus MPDL3280A + bevacizumab versus sunitinib	Untreated metastatic ccRCC	PFS	ORR, duration of response, OS, safety
Pembrolizumab (MK-3475)	NCT02014636	1/2	Pembrolizumab versus pazopanib + pembrolizumab versus pazopanib	Untreated advanced ccRCC	AEs, PFS	ORR, OS, duration of response
	NCT02089685	1/2	Pembrolizumab + peg-IFN versus pembrolizumab + ipilimumab versus pembrolizumab	Advanced melanoma, previously treated advanced ccRCC	DLT, AEs, PFS	ORR, duration of response, OS
Medi-4736	NCT02133742	1b	Pembrolizumab and axitinib	Untreated advanced RCC	DLT	Duration of response, ORR, PFS, OS
	NCT01938612	1	Medi-4736	Japanese patients with advanced solid tumors	DLT, safety	ORR, OS, PFS, pharmacokinetics
Pidilizumab (CT-011)	NCT01693562	1	Medi-4736	Advanced solid tumors	DLT, ORR	OS, PFS
	NCT01441765	2	Pidilizumab versus pidilizumab + DC vaccine	Metastatic RCC	AEs, response rate	Immunological response, OS
AMP-224	NCT01352884	1	AMP-224	Advanced solid tumors	AEs, DLT	ORR, pharmacokinetics, PD-L1 expression

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

AEs adverse events, *ccRCC* clear cell renal cell carcinoma, *DC* dendritic cell, *DLT* dose-limiting toxicity, *IFN* interferon, *IL* interleukin, *ORR* objective response rate, *OS* overall survival, *PD-L1* programmed cell death ligand-1, *peg-IFN* peginterferon, *PFS* progression-free survival

^aThe NCT numbers are ClinicalTrials.gov identifiers