Programmed Death-1 Inhibition in Renal Cell Carcinoma: Clinical Insights and Future Directions

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Abstract: The treatment of metastatic renal cell carcinoma (mRCC) has evolved markedly over the past decade, broadening beyond immune-based strategies (eg, interleukin-2 and interferon-α) to include targeted agents (eg, sunitinib [Sutent, Pfizer] and sorafenib [Nexavar, Bayer]). Recently, there has been a renewed interest in immune-based strategies, with clinical trials underway to assess vaccines and other immunomodulatory agents. Of particular interest are agents that inhibit the interaction between the programmed death-1 (PD-1) receptor and its ligand (PD-L1) at the T-cell/antigen-presenting cell interface. This interaction produces T-cell anergy and therefore stifles the antitumor immune response. Monoclonal antibodies to PD-1 (eg, nivolumab, lambrolizumab, and pidilizumab) and PD-L1 (MPDL3280A and BMS-936559) are in various stages of clinical development. The clinical trajectory of these agents is discussed herein, with specific attention to the potential placement of PD-1/PD-L1 inhibition in the crowded therapeutic landscape of mRCC.

Introduction

The pattern of drug development for metastatic renal cell carcinoma (mRCC) has followed a rather consistent trend over the past several years. This trend was predicated on the well documented role of vascular endothelial growth factor (VEGF)—a moiety that stimulates tumor angiogenesis—as a key driver of RCC progression.[1] Multiple agents have been approved that abrogate VEGF-mediated signaling through a variety of mechanisms. For instance, the monoclonal antibody bevacizumab (Avastin, Genentech) binds VEGF ligand, preventing receptor binding.[2] The small molecule VEGF-tyrosine kinase inhibitors (VEGF-TKIs) inhibit the intracellular catalytic domain of the VEGF receptor (VEGFR). These drugs include sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer and Onyx), axitinib (Inlyta, Pfizer) and pazopanib (Votrient, GlaxoSmithKline).[3-6] Finally, 2 approved agents in mRCC (everolimus [Afinitor, Novartis] and temsirolimus [Torisel, Wyeth]) target a downstream mediator of VEGF signaling, namely the mammalian target of rapamycin (mTOR).[7,8]
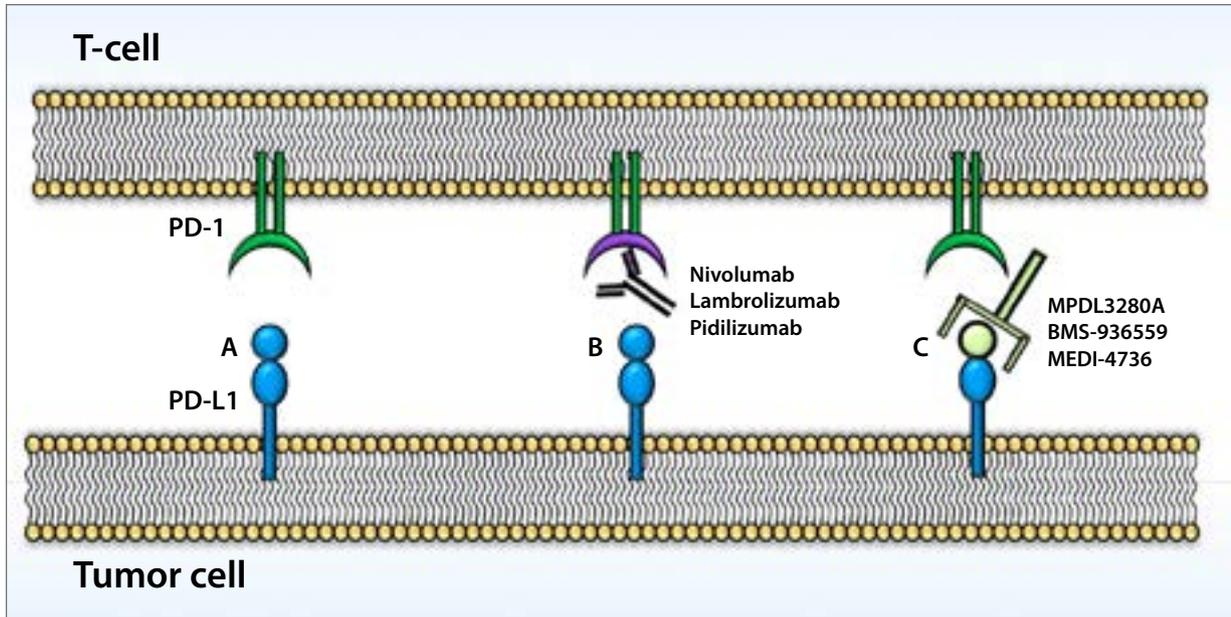
Figure 1. Pharmacologic strategies to achieve programmed death-1 (PD-1) inhibition. PD-1 on the T-cell surface interacts with its ligand (PD-L1) on the tumor cell or antigen-presenting cell, inducing T-cell anergy and stifling the antitumor immune response (A). Monoclonal antibodies directed at PD-1 include nivolumab, lambrolizumab and pidilizumab (B). Monoclonal antibodies directed at PD-L1 include MPDL3280A, BMS-936559, and MEDI-4736 (C).

The drug development paradigm centered on VEGF appears to be changing. Specifically, the VEGF-TKI tivozanib failed to garner FDA approval.[9] Tivozanib had been assessed in the TIVO-1 (Tivozanib Versus Sorafenib in First-Line Advanced RCC) trial, comparing tivozanib and sorafenib in treatment-naive patients. The study met its primary endpoint, showing a modest improvement in progression-free survival (PFS) with tivozanib. However, questions around overall survival (OS) marred the study, and the Oncology Drug Advisory Committee (ODAC) recommended against approval on this basis.[10] Certainly, this verdict does not bode well for VEGF-directed therapies under development in mRCC, such as regorafenib and ramucirumab.[11,12] However, these developments do shift focus toward agents that exercise a unique mechanism of action. There are many such agents in both early and late phase studies. For instance, MET-pathway inhibitors such as ARQ197 and cabozantinib have shown activity in patients with heavily pretreated mRCC. The novel small molecule sonepcizumab blocks sphingosine-1-phosphate receptor-1 (S1PR1), which the current authors have implicated in RCC pathogenesis.[13,14] Perhaps the greatest enthusiasm, however, has surrounded the development of novel immune-based therapies for mRCC. Since the approval of interleukin-2 (IL-2) more than 2 decades ago, investigators have sought other agents to augment the antitumor immune response in mRCC.[15] As monotherapy, the CTLA4-blocking agents tremelimumab and ipilimumab (Yervoy, Bristol-Myers Squibb) have shown

only modest activity at best.[16,17] However, over the past 2 years, agents inhibiting programmed death-1 (PD-1) and its ligands have shown exceptional activity in RCC (Figure 1). Herein, the biology and clinical data associated with these agents are reviewed. Furthermore, the clinical positioning of these agents amidst existing therapies for mRCC is described.

Rationale for PD-1 Inhibition

PD-1 is a cell surface glycoprotein expressed on a diverse array of hematopoietic cells.[18] Dysregulation of the PD-1 appears to have a marked effect on immune function. For example, BALB/c-PD-$1^{-/-}$ mice develop a severe cardiomyopathy owing to an increase in antibodies directed at cardiac myocytes.[19] In a different model, C57BL/6 PD-1–deficient mice were shown to have splenic enlargement with an increase in myeloid cells. Furthermore, C57BL/6-PD-$1^{-/-}$ mice develop arthritides and glomerulonephritis.[20]

Two known ligands for PD-1 exist: PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273).[21] PD-1 expressed on the surface of T cells interacts with PD-L1 on the surface of antigen presenting cells (APCs), thereby promoting T-cell anergy and stifling the antitumor immune response.[22-24] The role of PD-1 as a prognostic marker has been examined across a multitude of malignancies. For instance, in non–small-cell lung cancer (NSCLC) and gastric cancer, tumor expression of PD-L1 expression has been tied to decreased survival.[25] In a series including 196

Table 1. PD-1 Inhibitors Currently Under Investigation

Name	Description	Development Status
Nivolumab (BMS-936558, MDX-1106)	IgG4 monoclonal antibody	Phase 1 data in melanoma, mCRPC, NSCLC, mRCC, and mCRC completed No DLTs 34 patients with mRCC assessed RR: 29% Median duration of response: 12.9 months 6-month PFS: 58% Phase 1 study ongoing to assess combination with sunitinib, pazopanib, or ipilimumab in mRCC Phase 3 study (nivolumab vs everolimus) recently initiated in mRCC Multiple studies ongoing in other malignancies
Lambrolizumab (MK-3475)	IgG4 monoclonal antibody	Phase 1 study in solid tumors completed Patients with melanoma, mCRC, NSCLC, and carcinoid assessed No DLTs Expansion cohort in melanoma complete Randomized phase 2 study in melanoma (lambrolizumab vs cytotoxic therapy) ongoing Phase 2/3 study in NSCLC (lambrolizumab vs docetaxel) ongoing No further studies in mRCC currently available
Pidilizumab (CT-011)	IgG1 monoclonal antibody	Phase 1 study in hematologic malignancies completed No DLTs Combination with gemcitabine being assessed in resected pancreatic cancer Combination with autologous dendritic cell vaccine currently underway in mRCC
AMP-224	PD-L2/IgG1 fusion protein	Phase 1 study completed in solid tumors and cutaneous T-cell lymphoma, results pending

DLT, dose-limiting toxicity; mCRC, metastatic colorectal cancer; mCRPC, metastatic castration-resistant prostate cancer; mRCC, metastatic renal cell carcinoma; NSCLC, non–small-cell lung cancer; PFS, progression-free survival; PD, programmed death.

patients with clear cell RCC, nephrectomy specimens were stained for PD-L1 with anti-human B7-H1 monoclonal antibody.[26] Expression of PD-L1 was correlated with advanced stage, grade, and the presence of sarcomatoid differentiation. On univariate analysis, cancer-specific mortality was higher in patients with PD-1–expressing immune cells (hazard ratio [HR], 2.24; P=.004).

There is a compelling rationale to utilize PD-1 inhibition as a therapeutic strategy. Blank and colleagues utilized the B16-F10 melanoma model, which is weakly immunogenic.[27] Treatment with interferon-γ (IFN-γ) did result in an increase in surface antigens; however, these cells were still unresponsive to primed T cells. In contrast, primed T cells derived from $PD-1^{-/-}$ mice did result in tumor rejection. Iwai and associates have demonstrated an antimetastatic effect of PD-1 inhibition through antibody treatment. Specifically, decreased migration of B16 melanoma and CT26 colorectal cancer cells were noted to the liver and lung, respectively, in immunocompetent murine models.[28] Similarly, Okudaira and coworkers demonstrated antitumor activity of PD-1 antibodies in the setting of Panc02 pancreatic cancer cells in C57BL/6 mice.[29] Several preclinical studies have also suggested potential synergy between other immunotherapeutic approaches and PD-1 inhibition. For instance, Webster and colleagues

have shown that treatment of murine xenograft models bearing murine renal cell carcinoma (RENCA) tumors respond better to the combination of PD-1 inhibition and tumor cell vaccination when compared with either strategy alone.[30] These data underscore current efforts to combine PD-1 inhibitors with other immune-directed therapies, as discussed later in this manuscript.

PD-1 Inhibitors Currently in Development

Nivolumab (BMS-936558, MDX-1106)

Among the PD-1 inhibitors currently under investigation, the monoclonal antibody nivolumab is furthest along in clinical development (Table 1). Nivolumab has a high affinity for PD-1 (K_d = 2.6 nmol/L), and prevents the interaction of PD-1 with both PD-L1 and PD-L2. The first published phase 1 experience with nivolumab included patients with 5 disease types: metastatic melanoma, metastatic castration-resistant prostate cancer (mCRPC), NSCLC, mRCC, and metastatic colorectal cancer (mCRC).[31] Patients eligible for the study were those with treatment-refractory disease, and the concurrent use of immunosuppressive therapies (ie, corticosteroids) was not permitted. Patients received a single dose of nivolumab (at 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg), with weekly monitoring for a period of 8

weeks. If clinical benefit was observed during radiographic evaluations at 8 and 12 weeks, then 2 additional doses of nivolumab could be rendered.

No dose-limiting toxicities (DLTs) were observed in this experience, nor was a maximally tolerated dose (MTD) noted; thus, a dose expansion cohort comprised of 15 patients was established at 10 mg/kg.[31] Ultimately, a total of 39 patients were treated, with a median of 4 prior therapies. The largest subset was comprised of mCRC patients (n=14), followed by melanoma (n=10), mCRPC (n=8), and NSCLC (n=6). Only 1 patient with mRCC was enrolled. A total of 3 responses were encountered. More specifically, 1 patient with mCRC treated with 3 mg/kg had a complete response (CR). An additional 2 patients treated with 10 mg/kg had partial responses (PRs)—these patients had mRCC and NSCLC, respectively. Notably, the patient with mRCC who incurred a PR had a mixed response at first, evolving to a PR after 2 additional doses of nivolumab.

From a limited subset of patients enrolled in this study, tumor biopsies were available. Four out of 9 patients had prominent expression of PD-L1, and 3 of these patients had responses to nivolumab.[31] In contrast, among 5 patients with low PD-1 expression, no responses were observed. Biopsy specimens were available for comparison before and after treatment with nivolumab in 2 patients. In 1 of these patients, it was noted that treatment with nivolumab resulted in infiltration of CD8-positive T cells in tumor tissue. Pharmacokinetic studies accompanying this phase 1 trial suggested a half-life for nivolumab of approximately 12 days at lower doses (0.3-3 mg/kg) and 20 days at higher doses (10 mg/kg). Receptor occupancy appeared to be dose independent, and occupancy decayed after approximately 85 days.

On the basis of the encouraging efficacy signals noted in this study, a larger phase 1b trial was launched.[32] Patients with the same disease subtypes were enrolled, but the dose of 0.3 mg/kg (noted to have little activity in the previous study) was omitted. Patients were thus treated with doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg. A second key difference in the phase 1b experience was the duration and frequency of therapy. Patients were treated every 2 weeks for up to 2 years. In this study, no DLTs were observed, and thus expansion cohorts including 16 patients each were enrolled at doses of 10 mg/kg across all 5 disease subtypes. Given preliminary activity at lower doses, expanded cohorts were developed allocating melanoma patients to either 1 mg/kg or 3 mg/kg; NSCLC patients to 0.1 mg/kg, 0.3 mg/kg, or 1 mg/kg; and mRCC patients to 1 mg/kg.

Data from the subset of patients with mRCC (n=34) were recently updated.[33] This cohort of patients was heavily pretreated, with 44% of patients receiving at least 3 prior therapies. Prior antiangiogenic therapies were most com-

mon (74%), although a substantial proportion of patients (59%) had received immune-based treatments. A total of 10 responses were observed (29%), with similar response rates in patients treated with 1 mg/kg and 10 mg/kg (28% and 31%, respectively). Among the 10 responders, the median duration of response was 12.9 months. The rate of PFS at 6 months was 58% in the subset overall, and again similar at the 1 mg/kg and 10 mg/kg doses (50% and 67%, respectively). Impressively, median OS has not yet been reached for this heavily pretreated cohort.

Safety data for nivolumab specific to the mRCC cohort were also recently reported. The rate of grade 3/4 toxicity was 21%, including hypophosphatemia and respiratory disorders.[33] For the overall study population (n=296), the rate of grade 3/4 toxicity was only 14%, including pneumonitis, diarrhea, pruritus, macular rash, and an array of laboratory abnormalities.[32]

Although biomarker data have not been reported specifically within the subset of patients with mRCC, there was an effort to characterize PD-L1 expression in the overall study population.[32] Interestingly, no responses were observed among 17 patients with no cell surface expression of PD-L1, mirroring the previous phase 1 trial. In contrast, 9 of 25 patients (36%) with PD-L1 expression were characterized as responders. These studies belie the potential value of PD-L1 as a predictive biomarker. Nevertheless, this would require substantial prospective validation.

Given the encouraging data observed in the setting of mRCC, several future trials are planned. In a phase 3 study that may lead to regulatory approval (NCT01668784), patients with mRCC will be randomized to nivolumab (3 mg/kg intravenously every 2 weeks) or everolimus (10 mg orally per day; Figure 2).[34] Key eligibility criteria for the trial include the presence of a clear cell component, 1 or 2 prior antiangiogenic therapies, and no more than 3 prior therapies. The study will include a total of 822 patients, and will evaluate the primary endpoint of OS. Secondary endpoints include PFS, response rate, and safety. A second clinical trial of great interest is evaluating 3 combinations of nivolumab with other targeted therapies (NCT01472081).[35] Although originally designed to evaluate the combination of nivolumab with sunitinib or pazopanib, a third arm was added to evaluate the combination of nivolumab with ipilimumab (Figure 3). Ipilimumab, a monoclonal antibody directed at the CTLA4 receptor, has gained approval in the setting of metastatic melanoma, and the combination of nivolumab with ipilimumab in the same disease has recently demonstrated remarkable efficacy.[36]

Lambrolizumab (MK-3475)

Lambrolizumab is a distinct PD-1–directed monoclonal antibody. The antibody has high affinity for PD-1, with a
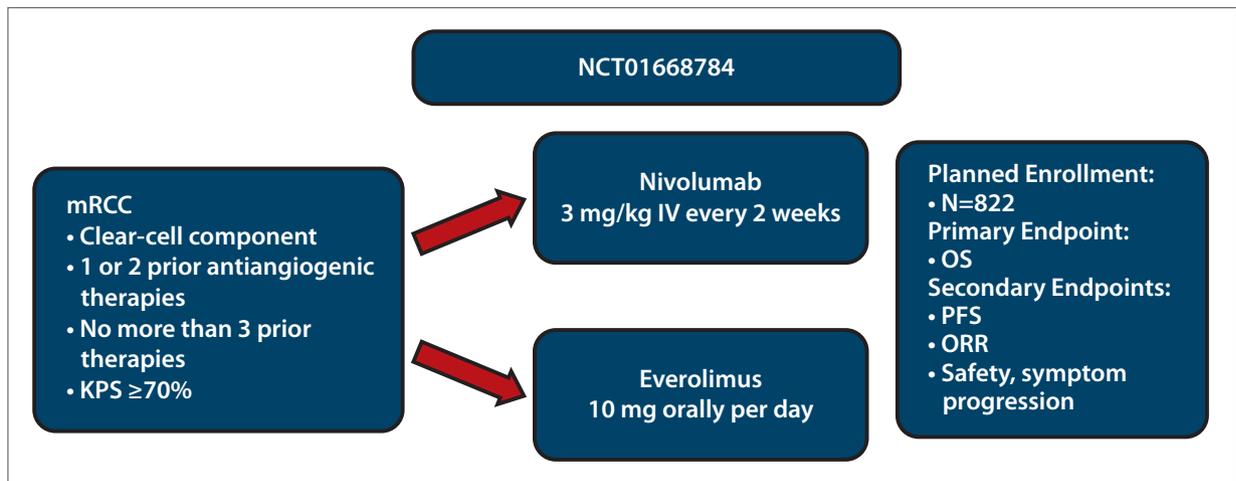
Figure 2. A randomized, phase 3 trial comparing nivolumab and everolimus in patients with metastatic renal cell carcinoma.

IV, intravenously; KPS, Karnofsky performance score; mRCC, metastatic renal cell carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
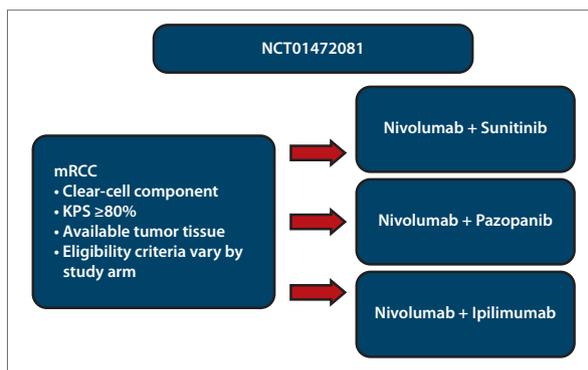
Figure 3. A phase 1 trial evaluating the combination of nivolumab with sunitinib, pazopanib, or ipilimumab.

KPS, Karnofsky performance score; mRCC, metastatic renal cell carcinoma.

K_d of approximately 29 pM.[37] The phase 1 evaluation of lambrolizumab was performed at a single center, enrolling patients with advanced solid tumors. Patients were treated with 1 of 3 dose levels of lambrolizumab (1 mg/kg, 3 mg/kg, or 10 mg/kg intravenously), with the second dose of the drug administered on day 29 of therapy, and every 2 weeks thereafter. Ultimately, 5 patients with NSCLC, 3 patients with melanoma, 3 patients with mCRC, and 2 patients with carcinoid tumors were enrolled; 4 additional patients had unspecified tumors. The majority of patients (78%) had received 4 or more prior lines of therapy. Fatigue, pruritus, and dyspnea were the most commonly observed adverse events; pruritus was the most common drug-related adverse event and was noted early after the first infusion with lambrolizumab. Grade 3/4 toxicities were infrequent, and no DLTs were observed. There was 1 patient who developed pneumonitis, with no findings of infection or malignancy on further evaluation of pulmonary radiographic findings.

Pharmacokinetic analyses suggested a half-life ranging from 14 to 21 days.[37] Response data were most impressive in the subset of patients with melanoma, with 2 patients incurring confirmed PRs, and 1 additional patient with an unconfirmed PR. One patient with NSCLC was also noted to have an unconfirmed PR.

On the basis of the impressive data noted in the setting of melanoma, an expansion cohort restricted to patients with melanoma was generated.[38] In this cohort, lambrolizumab was administered at 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks. A total of 117 patients were included in this expansion cohort, with a confirmed objective response rate of 44% and a median duration of response ranging from 1.9 to 10.8 months. Several studies are currently underway to further assess lambrolizumab. A randomized, phase 2 clinical trial will compare lambrolizumab with chemotherapy in patients with advanced melanoma.[39] In the setting of NSCLC, a phase 2/3 study will compare lambrolizumab with docetaxel.[40] Other studies will evaluate lambrolizumab in mCRC. However, there are no reported plans to develop the agent further in mRCC.[41]

Pidilizumab (CT-011)

While pidilizumab is also a monoclonal antibody directed at PD-1, the clinical development of the agent differs from that of nivolumab and lambrolizumab. Specifically, the phase 1 study of pidilizumab was confined to patients with hematologic malignancies, including acute myeloid leukemia (AML), multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia.[42] A single dose of pidilizumab ranging from 0.2 to 6 mg/kg was administered to a total of 17 patients. No DLTs were encountered in this experience, with the most frequent toxicities including diarrhea, rash, and back pain. Median OS in the study was 25 weeks.

Table 2. PD-L1 Inhibitors Currently Under Investigation

Name	Description	Development Status
MPDL3280A (RG7446)	IgG1 engineered monoclonal antibody	Phase 1 study in advanced solid tumors No DLTs Expansion cohorts established in mRCC, NSCLC, and melanoma 55 patients with mRCC assessed RR of 13% in 47 evaluable patients RR of 20% in patients with PD-L1 expression RR of 10% in patients with no PD-L1 expression Combination with FOLFOX-A or bevacizumab being assessed in mCRC Combination with vemurafenib being assessed in *BRAF*-mutated melanoma No further studies in mRCC currently available
BMS-936559 (MDX-1105)	IgG4 monoclonal antibody	Phase 1 study in NSCLC, melanoma, ovarian cancer, mCRC, pancratic cancer, gastric cancer, breast cancer, and mRCC completed No DLTs 17 patients with mRCC assessed RR of 12% Both patients treated at 10 mg/kg 41% of patients with stable disease at 6 months No further studies in mRCC currently available
MEDI4736	Monoclonal antibody	Phase 1 study ongoing in melanoma, NSCLC, mRCC, and mCRC

DLT, dose-limiting toxicity; FOLFOX-A, 5-fluorouracil, oxaliplatin, leucovorin, and bevacizumab; IgG, immunoglobulin G; mCRC, metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1; RR, response rate.

Although this initial experience with pidilizumab did not include patients with solid tumors, there are several efforts underway to assess the agent in several such disease types. A pilot study is current underway to evaluate the combination of pidilizumab in gemcitabine in patients with resected pancreatic cancer.[43] In the setting of mRCC, a study is currently underway to assess the combination of pidilizumab with a novel dendritic cell vaccine.[44] This phase 2 trial will include a total of 44 patients with measurable disease and a life expectancy exceeding 3 months. Two groups will be included in the trial. The first group will receive pidilizumab at a dose of 3 mg/kg intravenously on days 1, 14, and 28 of a 6 week cycle, for a total of 4 cycles. The second group will include patients who are undergoing cytoreductive nephrectomy. Patients in this cohort will receive infusions of an autologous dendritic cell vaccine generated with use of the nephrectomy specimen. The vaccine will be administered once during cycles 2 through 4 of pidilizumab therapy.

Clinical Strategies for PD-1 Inhibition: PD-L1 Antibodies

MPDL3280A (RG7446)

Aside from direct inhibition of PD-1, inhibition of PD-L1 may promote T-cell anergy (Table 2). The PD-L1 antibody MPDL3280A was evaluated in a population of patients with metastatic solid tumors.[45] Patients with measurable disease and an Eastern Cooperative Oncology Group performance status of 0 or 1 received MPDL3280A intravenously every 3 weeks for a period of 1 year, with follow-up every 12 weeks thereafter until the time of progression. No DLTs were observed at doses ranging from 0.3 to 20 mg/kg, and a phase 1a expansion study was performed in selected malignancies using doses of 10 mg/kg, 15 mg/kg, and 20 mg/kg. The malignancies selected for expansion included mRCC, NSCLC, and melanoma.

Data from the cohort of patients with mRCC were recently presented. Ultimately, a total of 55 patients with mRCC were enrolled.[45] Although the majority of patients had clear cell histology, the study did include 4 patients (7%) with papillary histology and 2 patients (4%) with predominantly sarcomatoid disease. Patients received a median of 2 prior therapies, (range, 0 to 7 treatments). Among mRCC patients, the most frequent toxicities were fatigue, arthralgias, cough, pyrexia, and constipation. Grade 3/4 toxicities occurred in 28 patients (43%), and included hyperglycemia, dyspnea, fatigue, hypophosphatemia, and hypoxia. Grade 3/4 events attributed to protocol-based therapy were infrequent, occurring in only 7 patients (13%).

In the overall study population (140 patients with multiple malignancies), a response rate of 21% was achieved.[45] In contrast, the response rate in evaluable patients with mRCC (n=47) was 13%. In the subset of 6 patients with nonclear cell histology, 1 response was observed. Expression of PD-L1 was evaluated in baseline tumor specimens. Among patients with mRCC, 2 of 10 patients (20%) with PD-L1

expression had documented responses, compare with only 2 of 20 patients (10%) with no PD-L1 expression. Notably, in the overall study population, there was a greater distinction in response based on PD-L1 expression. Specifically, the response rate was 36% in PD-L1–expressing patients, compared with 13% in patients with no PD-L1 expression. Several studies are planned to assess MPDL3280A as a single agent or in combination with other targeted therapies. In the setting of mCRC, 5-fluorouracil, oxaliplatin, leucovorin, and bevacizumab (FOLFOX-A) will be assessed, along with bevacizumab with MPDL3280A.[46] MPDL3280A will also be assessed with vemurafenib (Zelboraf, Hoffmann-La Roche) in patients with *BRAF*-mutated melanoma.[47] Experts have proposed combinations of MPDL3280A with VEGF-directed therapies, although the schema and design for such studies are not yet publicly available.

BMS-936559 (MDX-1105)

Similar to the phase 1 evaluation of nivolumab, the phase 1 evaluation of the PD-L1 antibody BMS-936559 was performed across a wide range of malignancies, including NSCLC, melanoma, ovarian cancer, mCRC, pancreatic cancer, gastric cancer, breast cancer, and mRCC.[48] Patients had at least 1 prior course of systemic treatment. Notably, this trial permitted stable brain metastases.

Patients were treated with doses of 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg.[48] Of the 207 patients enrolled, 17 had mRCC. Fatigue, infusion reactions, diarrhea, arthralgia, and rash were among the most common toxicities reported. The rate of grade 3/4 toxicity across the overall study population was 9%. Among patients with mRCC, 2 patients (12%) demonstrated responses. Both patients were treated with the 10 mg/kg dose. An additional 7 patients (41%) had stable disease at 6 months. Pharmacokinetic studies suggest a dose-dependent increase in BMS-936559 levels. The half-life was estimated to be approximately 15 days, with a median receptor occupancy of 65%. Despite the modest activity noted with this agent, there are no future dedicated trials in mRCC.

PD-1/PD-L1–Directed Therapies in Early Development

Several other PD-1/PD-L1–directed therapies are in early stages of clinical development. A phase 1 trial is currently underway to evaluate MEDI-4736, a monoclonal antibody directed at PD-L1.[49,50] The study will enroll patients with 1 of 4 solid tumors: melanoma, mRCC, NSCLC, and mCRC. Two dosing schedules of the agent (either every 2 weeks or every 3 weeks intravenously) will be evaluated. Patients must have measurable disease and archived tumor specimens. Planned correlative studies include pharmacokinetic assessment, antidrug antibody formation, and immune-related response.

A novel strategy for inhibiting PD-1 signaling is exemplified by AMP-224. This molecule is a recombinant B7-DC-Fc fusion protein that modulates PD-1 expression on T cells.[51] Mkrtichyan and colleagues demonstrated that AMP-224 was unable to directly block the PD-1/PD-L1 interaction. Instead, following the administration of AMP-224, the population of dysfunctional, PD-1^{HI} T cells was reduced, which led to increased immune response and tumor regression. As with several vaccine therapies (eg, AGS-003), it was noted that the combination of AMP-224 and cyclophosphamide synergistically enhanced the immune response, with more extensive tumor T-cell infiltration.[52] At present, a phase 1 study evaluating the compound has completed enrollment, but data from the study are still forthcoming. In the dose-escalation phase, the study eligibility included any patient with solid tumors or cutaneous T-cell lymphoma. An expansion phase was developed to include patients with refractory melanoma or ovarian cancer. Tissue collection for correlative analyses was required for both the dose escalation and expansion cohorts, and flow cytometric assessments of immune populations are planned. Data from this study are eagerly awaited.

Clinical Challenges

The data cited herein allude to an aggressive development plan for PD-1/PD-L1 inhibition in oncology, with certain agents progressing more rapidly than others in the space of mRCC. Among the agents described, nivolumab is clearly the furthest along in clinical development in mRCC, with a phase 3 study underway that could lead to regulatory approval. If this comparison of nivolumab to everolimus demonstrates an improvement in OS with nivolumab (sufficing the primary endpoint of the study), it may challenge the current sequencing paradigm for mRCC. After failure of a first-line VEGF-directed therapy, phase 3 data support either everolimus or axitinib therapy.[8,53] Positive data for nivolumab in the aforementioned trial would certainly push everolimus back in the current sequencing strategy, and on account of the favorable toxicity profile of nivolumab, axitinib may be pushed further back as well. Ultimately, further exploration of predictive biomarkers will be of essence. In the small correlative experiences previously cited, PD-L1 expression in tumor tissue was suggested to be a putative biomarker for response to PD-1/PD-L1 inhibitors. If larger studies offer validation, individuals with high PD-L1 expression could be selected for treatment with these agents.

Emerging prospective and retrospective datasets suggest that approximately 50% of patients with mRCC will not receive second-line therapy, making the first-line setting a critical opportunity for optimal therapy.[54,55] To

this end, no definitive studies are underway to compare PD-1/PD-L1 inhibition with VEGF-directed therapy (the most common first-line approach). However, the previously noted phase 1 study evaluating the combination of nivolumab with sunitinib, pazopanib, or ipilimumab may offer a pathway for PD-1 inhibitors to enter this therapeutic space. If the combinations of nivolumab with sunitinib and/or pazopanib are deemed to be safe and tolerable, comparative studies examining these VEGF-TKIs with or without nivolumab can be envisioned. This will require a great deal of resources, however. Phase 3 data will be required in order for the combination of VEGF-directed therapy with PD-1/PD-L1 to supersede VEGF-directed therapy alone in therapeutic algorithms. The path forward for the combination of ipilimumab with nivolumab is more arduous, since ipilimumab has only modest documented activity in mRCC as a single agent.[17] Even if data from the phase 1 experience are promising, the ipilimumab/nivolumab regimen will likely need to be compared with monotherapy using VEGF- or mTOR-directed agents.

Rational combinations will likely be the subject of further study with PD-1/PD-L1 inhibitors beyond nivolumab. It is anticipated that trials assessing MPDL3280A with VEGF-directed agents may emerge. The noted trial of pidilizumab with an autologous dendritic cell vaccine is also of substantial interest, especially with emerging vaccine-based therapies, such as AGS-003 and IMA901.[56-58] As more of these agents are examined in mRCC, the obvious question arises: which agent should be used preferentially to antagonize PD-1/PD-L1? Although trials comparing PD-1/PD-L1 inhibitors with other classes of therapy have been noted herein, it may ultimately be necessary to compare PD-1/PD-L1 inhibitors against each other in a head-to-head fashion. As the therapeutic landscape becomes saturated with these agents, one can envision that the process of regulatory approval may become increasingly competitive. History has delivered such lessons. For instance, the regulatory bar was perhaps raised for tivozanib in mRCC on account of the multiple, already-approved VEGF-TKIs.

The regulatory bar for mRCC may have to change in order to accommodate the anticipated clinical outcomes with PD-1/PD-L1 inhibitors. The immunomodulatory effect of these drugs may trigger latent—as opposed to immediate—responses. Anecdotal evidence suggests that modest tumor growth may be observed prior to tumor shrinkage. Thus, emerging protocols evaluating PD-1/PD-L1 inhibitors may actually permit treatment beyond progression.[59] As such, standard endpoints like PFS may be misleading in the context of these therapies. Melanoma investigators who have recognized the unusual response patterns associated with these novel immunotherapeutic strategies have devised a new method of drug evaluation, known as immune-related response criteria (irRC).[60] The

irRC criteria are distinguished from traditional Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria for progression in that they account for the size of new lesions on imaging studies (as opposed to RECIST or WHO, which consider any new lesions to be progressive disease). In addition, confirmatory scans are obtained not just for cases documented as a response, but also for cases recorded as progressive disease. This is a means of capturing latent responses. The irRC may be appropriate in mRCC in the context of comparative studies evaluating 2 distinct immunotherapeutic strategies (eg, comparison of a PD-1 inhibitor with a PD-L1 inhibitor). However, it is challenging to envision these criteria in the context of studies juxtaposing these immunotherapeutic strategies against more traditional targeted approaches (eg, VEGF-directed agents).

If complex definitions of response (such as irRC) challenge the use of traditional endpoints, what is the way forward for clinical trial endpoints in RCC? OS may represent the new standard primary endpoint in forthcoming clinical trials. However, if this is the case, special attention needs to be given to the confounding effect of therapies given after the study. For instance, in the ongoing trial of everolimus vs nivolumab, patients must have received VEGF-directed therapy, and may not have had everolimus therapy. Thus, patients exposed to nivolumab have the opportunity to potentially receive an active agent after the study (namely, everolimus), while patients randomized to everolimus may likely receive (in a somewhat redundant fashion) VEGF-directed therapies they have not yet been exposed to. Certainly, this may have a bearing on the ultimate outcome of this study.

Conclusions

The evolution of targeted therapies abrogating VEGF- and mTOR-mediating signaling has led to marked improvements in the prognosis of patients with mRCC.[61] However, the impact of these agents has reached somewhat of a plateau. The first-line evaluations of tivozanib and axitinib exemplify this phenomenon.[62,63] The experiences with PD-1 inhibition suggest an incredibly promising means of potentially breaking through this plateau. Although the data presented are largely from early-phase experiences with relatively small subsets of patients with mRCC, encouraging signals of activity have been seen within this group. The noted phase 3 studies evaluating nivolumab may represent the first of several large-scale efforts to validate the activity of PD-1/PD-L1 inhibitors in this disease. Assessments of combinations of PD-1/PD-L1 inhibitors with other approved agents for mRCC are in their infancy. Ultimately, these studies may allow for more seamless integration of PD-1/PD-L1 inhibitors in current clinical algorithms.

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