Prospects for Targeting PD-1 and PD-L1 in Various Tumor Types

In this review, we will discuss the current status of several anti-PD-1 and anti-PD-L1 antibodies in clinical development and their direction for the future.

What Are PD-1 and PD-L1?

Programmed death 1 (PD-1) is an immune inhibitory receptor expressed on several immune cells, particularly cytotoxic T cells.[1] It interacts with two ligands, programmed death ligand 1 (PD-L1) (B7-H1, CD274) and PD-L2 (B7-DC). While PD-L2 is expressed primarily on macrophages and dendritic cells, PD-L1 is expressed on tumor cells, as well as other immune cells. The interaction of these ligands with PD-1 inhibits T-cell activation and cytokine production. Their ligation with PD-1 during infection or inflammation in normal tissue is critically important in maintaining homeostasis of immune response to prevent autoimmunity. Their interaction in tumor microenvironments, however, provides an immune escape for tumor cells by turning off cytotoxic T cells.[2] Thus, blocking these interactions may subject the tumor cells to attack from cytotoxic T cells.

How Is PD-L1 Expression Determined? What Is Its Significance?

PD-L1 expression is measured most commonly by immunohistochemistry (IHC). Tumoral PD-L1 expression status has been shown to be prognostic in multiple tumor types, including melanoma (MEL), renal cell carcinoma (RCC), and non–small-cell lung cancer (NSCLC). In addition, tumoral PD-L1 expression appears to correlate closely with response to anti–PD-1 antibodies.[3] However, no test is uniformly accepted as the standard for quantitating PD-L1 expression. The IHC tests used in clinical trials are proprietary; data on similarities between and among the antibodies used and the assay conditions, staining pattern, threshold for signal detection, and assessment of positivity are not published. The protein expression patterns of PD-L1 on tumor cells, dendritic cells, and tumor-infiltrating immune cells differ, and exact cell type and degree of expression vary between assays. A different methodology for evaluating PD-L1 messenger RNA (mRNA) expression, using an antibody-independent in situ hybridization assay coupled with quantitative fluorescence, showed that increased PD-L1 mRNA transcript was associated with elevated tumor-infiltrating lymphocytes and better clinical outcomes in patients with breast cancer[4] and NSCLC.[5] The role of PD-L1 expression as a biomarker is discussed in this supplement to ONCOLOGY, in the review “Prognostic and Predictive Markers for the New Immunotherapies,” by Drs. Kathleen M. Mahoney and Michael B. Atkins.[6]

Anti–PD-1 and Anti–PD-L1 Antibodies

Several PD-1 and PD-L1 antibodies are in clinical development (Table 1). Overall, they are very well tolerated; most did not reach dose-limiting toxicity in their phase I studies. As listed in Table 2, no clinically significant difference in adverse event profiles has been seen between anti–PD-1 and anti–PD-L1 antibodies. Slightly higher rates of infusion reactions (11%) were observed with BMS-936559 (anti–PD-L1) than with BMS-96558 (nivolumab). In an early stage of a nivolumab phase I study, there was concern about fatal pneumonitis.[7] It has been hypothesized that PD-1 interaction with PD-L2 expressed on the normal parenchymal cells of lung and kidney provides unique negative signaling that prevents autoimmunity.[8] Thus, anti–PD-1 antibody blockage of such an interaction may remove this inhibition, allowing autoimmune pneumonitis or nephritis. Anti–PD-L1 antibody, however, would theoretically leave PD-1–PD-L2 interaction intact, preventing the autoimmunity caused by PD-L2 blockade. With implementation of an algorithm to detect early signs of pneumonitis and other immune-related adverse events, many of these side effects have become manageable. However, it does require discerning clinical attention to detect potentially fatal side effects. In terms
of antitumor activity, both anti–PD-1 and anti–PD-L1 antibodies have shown responses in overlapping multiple tumor types. Although limited to a fraction of patients, most responses, when observed, were rapid and durable.

**Metastatic Melanoma**

**Nivolumab**

MEL is among the first types of solid tumors in which nivolumab has shown promising antitumor activity. In a phase I study across all dose levels, nivolumab resulted in an objective response rate (ORR) of 28% (95% confidence interval [CI], 19–38) in patients with advanced MEL who had no prior ipilimumab treatment.[7] Responses were adjudicated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0, with modification. A recently updated analysis in 107 MEL patients confirmed these responses and suggested potential survival benefit.[9,10] The ORR was 32% (95% CI, not reported [NR]). The median duration of response was 99.4 weeks (range, 17.0+ to 117.0+). More than half (11/21) of responding patients who discontinued therapy for reasons other than progressive disease responded for more than 24 weeks. The 1-, 2-, and 3-year overall survival (OS) rates were 63% (95% CI, 53–71), 48% (95% CI, 38–57), and 41% (95% CI, 31–51), respectively. Median OS was 17.3 months (95% CI, 12.5–36.7). Survival analysis by type of response suggested that patients who had immune-related responses, such as reduction in the target lesion in the presence of new lesions or following initial progression, had similar OS to patients with RECIST responses.[9,10]

Nivolumab in patients who were pretreated with ipilimumab was tested as part of a “sequential cohort” of an ongoing phase I trial. Nivolumab was given at two dose levels (1 mg/kg and 3 mg/kg every 2 weeks). Of 33 patients, ORR by RECIST criteria was 31% (95% CI, NR). The 1-year survival rate was 70% (95% CI, NR). The residual plasma concentration of prior ipilimumab at the start of nivolumab appears to have an influence on response to nivolumab. An ipilimumab concentration ≥ 7.255 μg/mL (the median) was associated with greater ORR to nivolumab (57.1% vs 14.3%).[11]

**Pembrolizumab**

Pembrolizumab (MK-3475, lambrolizumab) is a humanized immunoglobulin G (IgG)-4 kappa antibody against PD-1. In KEYNOTE-001, the safety and antitumor activities of pembrolizumab were tested in the largest-ever phase I study of patients with metastatic MEL (N = 411).[12] This study began with ipilimumab-naive (IPI-N) and ipilimumab-treated (IPI-T) patients, and later implemented a randomized dosing comparison of 2 mg/kg vs 10 mg/kg in ipilimumab-refractory (IPI-R) and IPI-N patients. Among patients evaluable by RECIST 1.1, overall ORR was 34% (95% CI, 29–39). The ORRs were 40% (95% CI, 32–48) in IPI-N patients and 28% (95% CI, 22–35) in IPI-T patients. The 1-year OS rate was 69%; median OS has not yet been reached. A subgroup analysis suggested that a tumor size smaller than the median of 90 mm was an independent predictor of response.[13]

In the randomized comparison of 2 mg/kg vs 10 mg/kg of pembrolizumab in IPI-R and IPI-N patients,[14] there was no statistically significant difference between the ORRs for the two cohorts by either RECIST 1.1 (independent central review) or immune-related response criteria (investigator review). In the IPI-N cohort, the ORRs by RECIST 1.1 were 33% (95% CI, 20–49) vs 40% (95% CI, 26–56) in the 2-mg/kg and 10-mg/kg arms, respectively (P = .4835). In the IPI-R cohort, the ORRs were 26% in both arms (95% CI, 17–37 in the 2-mg/kg arm and 95% CI, 17–36 in the 10-mg/kg arm). According to Kaplan-Meier estimates of OS in IPI-N patients, 1-year OS rates were 72% (95% CI, 15–NR) and 64% (95% CI, 10–NR), and in IPI-R patients, they were 58% (95% CI, 11–NR) and 63% (95% CI, NR)—in the 2-mg/kg and 10-mg/kg arms, respectively. Given favorable benefit-risk profiles at both doses, 2 mg/kg every 3 weeks was recommended for future investigation. The most common immune-mediated adverse event of any grade was hypothyroidism (~8%). There was a < 1% incidence of grade 3 or 4 pneumonitis, hepatitis, colitis, or hypophysitis reported.

**Pidilizumab**

Pidilizumab is a humanized anti–PD1 IgG1 kappa with binding affinity at 20 nM. A phase II study in MEL patients showed ORR (by investigator review) of 7% in IPI-N patients and 5% in IPI-T patients.[15] The rate of immune-related stable disease was 37%. The 12-month survival rate was 64% (95% CI, 55.6–72.0). Pidilizumab is being investigated in hematologic malignancies.

**MPDL3280A**
MPDL3280A is an IgG1-engineered, anti-PD-L1 antibody. A phase I study in 38 patients with metastatic MEL reported a 39% ORR (95% CI, NR), with 43% achieving a 24-week progression-free survival (PFS).[16] Both patients with cutaneous (33%) and mucosal (25%) MEL responded. Patients with PD-L1-positive status by IHC had a 27% ORR (95% CI, NR). Similarly, patients with a negative status had a 20% ORR (95% CI, NR). An additional 60% of patients with PD-L1-positive tumors had stable disease, suggesting that PD-L1-positive patients are more likely to derive clinical benefit. No grade 3 or 4 pneumonitis or treatment-related deaths occurred. Based on these findings and a potential synergy with vemurafenib, a phase Ib study is currently testing the safety and tolerability of this combination in patients with BRAF V600E mutations (National Cancer Institute ClinicalTrials.gov ID NCT01656642).

BMS-936559

BMS-936559 is a fully human, anti-PD-L1, IgG4 monoclonal antibody. In a study of 1-, 3-, and 10-mg/kg doses in metastatic MEL patients, 9 of 52 (17%; 95% CI, 8–30) achieved objective responses.[17] Three patients achieved a complete response (CR). Five of 9 responding patients had an objective response lasting beyond 1 year. In addition, 14 of 52 patients (27%; 95% CI, 16–41) had stable disease lasting at least 24 weeks.

MEDI4736

MEDI4736 is an engineered IgG1 kappa monoclonal antibody with triple mutations in the Fc domain to remove antibody-dependent, cell-mediated cytotoxic activity. It has shown high affinity and selectivity for PD-L1 and, reportedly, no binding to PD-L2.[18] In its dose escalation study of doses ranging from 0.1 mg/kg every 2 weeks to 15 mg/kg every 3 weeks, no dose-limiting toxicity or drug-related deaths were seen. Tumor regression was seen in multiple tumor types, including MEL, NSCLC, RCC, and colorectal cancer (CRC). Segal et al reported the results of a multiarm expansion study using a dose of 10 mg/kg every 2 weeks in 44 patients with MEL (uveal and cutaneous).[19] Although an analysis of antitumor activity in MEL patients has not been reported, preliminary data suggest that several patients with both cutaneous and uveal MEL remained in the study beyond 12 weeks, and no serious adverse events have been reported.

Combinations

In light of their promising activity as single agents, several combinations of anti–PD-1 and anti–PD-L1 antibodies have been studied. A preclinical study has shown that dual immune checkpoint blockade of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1 resulted in more pronounced antitumor activity than either single blockade alone.[20] Wolchok et al reported the clinical activity of concurrent administration of nivolumab and ipilimumab in 53 patients with advanced MEL; the resulting ORR was 40% (95% CI, 27–55) (by modified World Health Organization [WHO] criteria), and responses were “rapid and deep.”[21] In an updated survival analysis, Sznol et al reported 1- and 2-year OS rates of 85% and 79% (95% CI, NR), respectively; median OS was 40 months, and median PFS was 27 weeks.[11] This study added another cohort of 40 patients who received nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 1 mg/kg every 3 weeks for 4 more cycles, then 3 mg/kg every 2 weeks for up to 48 cycles. Results confirmed clinical activity, with an ORR of 43% (95% CI, NR). Responses were seen regardless of PD-L1 tumor expression status or BRAF mutation status.

Nivolumab in combination with multiple peptide vaccines in IPI-R or IPI-N MEL patients was well tolerated.[22] This study also found that increased peripheral blood regulatory T cells and decreased antigen-specific T cells were associated with progression. The clinical benefit of adding a vaccine remains to be seen.

A phase I/II study of MEDI4736 in combination with a BRAF inhibitor (dabrafenib) and a MEK inhibitor (trametinib) or with trametinib alone is ongoing (NCT02027961). Other immune modulatory agents, such as interferon (IFN) alfa-2b, are combined with various anti–PD-1 and anti–PD-L1 antibodies in ongoing clinical trials.

Metastatic Renal Cell Carcinoma

Metastatic RCC (mRCC) has been a target of immunotherapy for several decades; high-dose interleukin-2 has shown an ORR of approximately 20%, with long-term remission in a small subset of patients,[23] and ipilimumab has shown an ORR of 12.5% (95% CI, 4–27).[24] Over the past decade, the US Food and Drug Administration (FDA) has approved several antiangiogenic agents for mRCC
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on the basis of improvement in PFS; however, none have demonstrated survival benefits.

Nivolumab
The activity of nivolumab in mRCC was reported in its first phase I study, in which 9 of 33 patients (27%; 95% CI, 13–46) achieved objective responses and 56% (95% CI, 39–73) were alive without disease progression at 24 weeks. At the time of data analysis, five of these responding patients had a response lasting for more than a year.[7] The clinical activity of nivolumab in mRCC was confirmed in a dose-ranging phase II study, in which patients were randomized to receive either 0.3, 2, or 10 mg/kg every 3 weeks.[25] Clinical activities were seen across all dose levels, with ORRs of 20%, 22%, and 20% (95% CI, NR), respectively. On survival analysis, median OS outcomes were 18.2 months (80% CI, 16.2–24.0), 25.5 months (80% CI, 19.8–28.8), and 24.7 months (80% CI, 15.3–26.0), respectively. These survival data appeared very promising in the context of other published median OS data of 12 to 16 months for mRCC in second-line settings.[26,27] In a phase III randomized controlled trial, nivolumab is being compared with everolimus in patients previously treated with antiangiogenic therapy; the primary outcome measure is OS (NCT01668784).

BMS-936559
In patients with mRCC, 2 of 17 (12%; 95% CI, 2–36) had an objective response to 10 mg/kg of BMS-936559, with responses lasting 4 and 17 months.[17] Seven additional patients (41%; 95% CI, 18–67) had stable disease lasting at least 24 weeks.

MPDL3280A
Cho et al reported that in 55 patients with mRCC, the anti–PD-L1 antibody MPDL3280A was very well tolerated, with no dose-limiting toxicities.[28] The overall ORR was 13% (95% CI, NR). Responses were seen in both clear-cell and non-clear-cell histology and in both PD-L1–positive and –negative patients. An additional 60% of patients had stable disease. At 24 weeks, 53% of the patients were alive without disease progression. In a phase II study, MPDL3280A is being assessed either as monotherapy or in combination with antiangiogenic agents (bevacizumab or sunitinib) in untreated mRCC (NCT01984242).

Combinations
To assess combination strategies, investigators have launched a large phase Ib multiarm combination study, CheckMate-016. Nivolumab plus ipilimumab was tested in a randomized study with different induction doses (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg [N3+I1] or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg [N1+I3], followed by nivolumab 3 mg/kg every 2 weeks for both arms. N1+I3 had a higher frequency (26%) of treatment-related adverse events leading to discontinuation, including elevations in lipase and alanine transaminase, diarrhea, and pneumonitis. The ORR was 43% (95% CI, 21.8–66.0) in the N3+I1 cohort and 48% (95% CI, 26.8–69.4) in the N1+I3 cohort[29]; these results appear to be more than additive effects. Approximately 80% of these responses were ongoing at the time of data analysis. An additional 24% of patients given N3+I1 and 36% given N1+I3 have achieved stable disease. The 24-week PFS rates were 64% to 65%. In 44 available samples, PD-L1 expression status did not correlate with response. With 1% tumor membrane staining as a cutoff, similar percentages of patients with PD-L1–positive and –negative tumors achieved objective responses (55% and 50%). Based on data supporting immune-suppressive effects of vascular endothelial growth factor (VEGF) and FDA-approved antiangiogenic agents for mRCC, nivolumab was tested in combination with either sunitinib (n = 33) or pazopanib (n = 20).[30] Both pretreated and treatment-naive patients responded. Overall confirmed ORRs were 52% (95% CI, 33.5–69.2) in the sunitinib combination arm and 45% (95% CI, 23.1–68.5) in the pazopanib combination arm. As seen with ipilimumab combinations, PD-L1 expression status, regardless of the staining cutoff, did not predict response to combination therapy with either sunitinib or pazopanib. The most common side effects were consistent with known toxicity profiles of these tyrosine kinase inhibitors and included diarrhea, fatigue, and hypertension. Two grade 3 pneumonitis events (3%) were observed.

Pembrolizumab
No pembrolizumab monotherapy data have been reported yet in patients with mRCC. Pembrolizumab is under investigation in combination with pazopanib in a phase I/II study (NCT02014636). In patients treated with pazopanib, increased PD-L1 expression was associated with...
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shorter PFS.

Non–Small-Cell Lung Cancer

The PD-1/PD-L1 pathway appears to be a critical therapeutic target for advanced NSCLC. Multiple PD-1 and PD-L1 antibodies have demonstrated antitumor activities in both pre- and postsystemic therapy settings. The activity appears to be more pronounced in earlier disease settings. As shown in Table 5, in chemotherapy-naive, PD-L–positive patients, nivolumab[31] and pembrolizumab[32] demonstrated ORRs of 50% (95% CI, NR) and 26% (95% CI, 14–42), respectively. In pretreated patients, nivolumab,[33] pembrolizumab,[34] MPDL3280A, [35] and MEDI4736[36] have demonstrated ORRs ranging from 16% to 23%.

Brahmer et al presented survival data of a phase Ib trial of nivolumab that included 129 heavily pretreated patients with advanced NSCLC, more than half of whom received > 3 prior therapies.[33] At a median follow-up of 27 months across all dose levels, 1- and 2-year OS rates were 42% (95% CI, 34–51) and 24% (95% CI, 16–32), respectively, and median OS was 9.9 months (95% CI, 9.8–12.4). Patients given the 3-mg/kg dose appeared to have superior survival data, with 1- and 2-year OS rates of 56% (95% CI, 38–71) and 45% (95% CI, 27–61), respectively, and a median OS of 14.9 months (95% CI, 7.3–NR). Unlike cytotoxic agents—and as seen in other settings, such as in mRCC[25]—nivolumab did not show a clear dose-response relationship in advanced NSCLC. The survival data are certainly encouraging in a disease where the median OS has been no more than 7 to 8 months.

PD-L1 expression on NSCLC tumor cells or tumor-infiltrating immune cells was associated with higher response rates. Although not statistically powered to show this, some degree of correlation has been observed with most of the agents, including pembrolizumab, MPDL3280A, and MEDI-4736. As noted in Table 5, across all these agents, except nivolumab in pretreated patients, PD-L1 expression was associated with higher response rates. ORRs were 23% to 46% vs 3% to 15% in PD-L1–positive vs PD-L1–negative groups, respectively.

As also noted, while PD-L1 expression was highly predictive of response to nivolumab in treatment-naive patients (50% in PD-L1–positive patients vs 0% in PD-L1–negative patients),[31] this was not the case for pretreated patients (15% in PD-L1–positive vs 14% in PD-L1–negative), using 5% as a PD-L1 expression cutoff.[33] This difference, despite the use of the same assay and the same drug, raises several questions, including questions of assay sensitivity, of archival tissue vs “fresh” pretreatment biopsy, and of whether the complexity of immune-mediated cytolysis is underestimated. Several ongoing phase III trials of nivolumab in advanced NSCLC require mandatory tissue samples and will explore the role of PD-L1 as a predictive biomarker for nivolumab, with its prespecified evaluation correlated to OS (see Table 7).

Another important potential predictive biomarker is smoking status. Both MPDL3280A[35] and pembrolizumab[34] have demonstrated higher response rates among current or former smokers than among never-smokers. Among current/former smokers, ORRs by RECIST 1.1 were 25% (95% CI, NR) and 26% (95% CI, 19–35) with MPDL3280A and pembrolizumab, respectively. Among never-smokers, ORRs were 16% (95% CI, NR) and 8% (95% CI, 3–18) with MPDL3280A and pembrolizumab, respectively. It has been hypothesized that because lung cancers in smokers are associated with more genetic mutations, they generate new tumor-associated or tumor-specific antigens, which are rendered more susceptible to recognition by immune cells. Thus, when an immune checkpoint such as PD-L1 is blocked, these patients’ immune cells may be more likely to respond and induce immune-mediated tumor cell killing.

Combination studies in NSCLC

Several combination strategies are being tested in large, multicohort phase I trials. Nivolumab, pembrolizumab, MEDI-4736, and MPDL3280A are being evaluated in combination with chemotherapies, oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, anti–CTLA-4 antibodies, or other targeted therapies.

Nivolumab and ipilimumab in combination were tested in chemotherapy-naive advanced NSCLC in the ongoing CA209-012 study.[37] At the time of data analysis, 8 of 29 patients (16%) had objective responses. Six of these patients (75%) had ongoing responses at the time of analysis. Most of the responses were seen by the time of the first tumor assessment (10 weeks). In an exploratory analysis based on PD-L1 status, responses were seen in both PD-L1-positive and PD-L1-negative patients, with ORRs of 19% (3/16) and 14% (3/22), respectively.

The CA209-012 study also tested nivolumab in combination with various platinum-doublet
chemotherapy regimens, including gemcitabine/cisplatin, pemetrexed/cisplatin, and paclitaxel/carboplatin. The safety data showed an adverse event profile reflecting the additive toxicities of nivolumab and chemotherapy. No dose-limiting toxicities were seen during the first 6 weeks of treatment.[38] ORRs were 33% (95% CI, 10–65) to 47% (95% CI, 21–73) across all arms.

One-year OS rates were 50% (95% CI, 21–74) to 87% (95% CI, 56–96). Nivolumab plus erlotinib was tested in 21 patients with chemotherapy-naive, EGFR-mutant, advanced NSCLC.[39] All except one patient had acquired resistance to the EGFR tyrosine kinase inhibitor. The overall ORR was 19% (95% CI, 5.4–41.9). Of 20 patients who had erlotinib resistance, 3 (15%) achieved a partial response. One erlotinib-naïve patient achieved a near CR, and all responses were durable beyond 78+ weeks. Nine patients (45%) had stable disease. The most common treatment-related adverse events were rash, fatigue, paronychia, diarrhea, and skin fissures. No pneumonitis of any grade was observed.

Bladder Cancer

Bladder cancer is another disease primed for PD-1 and PD-L1 blockade. Bladder cancer has been known to be an immune-responsive disease since the first use of bacillus Calmette-Guérin immunotherapy several decades ago.[40] Mullane et al reported PD-L1 expression status on 160 bladder tumor samples and found PD-L1 expression on mononuclear cells (37%) and tumor cells (20%).[41] Only PD-L1 expression on mononuclear cells was significantly associated with longer OS in patients who developed metastatic disease (P = .04). Sharma et al showed that the presence of CD8+ tumor-infiltrating lymphocytes in muscle-invasive bladder cancer was associated with longer disease-free survival (median, 13 months vs > 80 months; P < .001).[42] Furthermore, like NSCLC and MEL, bladder cancer has a high rate of somatic mutations,[43] which can potentially make it more susceptible to immune cell recognition and attack when the immune checkpoint is blocked. The first clinical data were reported from a phase I study of MPDL3280A in 67 patients with metastatic urothelial bladder cancer.[44] Approximately 80% of the patients had received cisplatin-based therapy, and 75% had visceral metastases. The overall ORR was 26%. The ORRs in patients with PD-L1-positive and PD-L1-negative status were 43% (95% CI, 26–63) and 11% (95% CI, 4–26), respectively. Median time to first response was 42 days (range, 38 to 85 days). Median duration of response was not reached. Sixteen of 17 responses were ongoing at the time of data cutoff. Based on these data, a single-arm phase II trial of MPDL3280A in patients with metastatic urothelial bladder cancer is enrolling patients into two cohorts: treatment-naive/cisplatin-ineligible and platinum-pretreated. The primary outcome measure is ORR (NCT02108652). Preliminary data from the phase Ib study of pembrolizumab were presented at the 2014 European Society for Medical Oncology Congress. Plimack et al reported that 7 of 33 (24%) patients achieved an objective response. Three patients (10%) achieved a CR.[45] A randomized phase III study is underway comparing pembrolizumab against standard second-line chemotherapies (docetaxel, paclitaxel, or vinflunine), with OS as a primary endpoint (NCT02256436). Other ongoing phase I trials of MEDI4736 and of nivolumab with or without ipilimumab are enrolling patients with urothelial tract cancer (NCT01693562, NCT01928394).

Squamous Cell Carcinoma of the Head and Neck

Head and neck squamous cell carcinoma (HNSCC) is another tumor well suited for PD-1 and PD-L1 blockade. Similar to lung and bladder cancers, it carries high mutation rates.[43] PD-L1 expression has been well documented, and the PD-1 pathway has been implicated in immune resistance in human papillomavirus (HPV)-associated HNSCC.[46] A gene expression signature study has shown that about one-third to one-half of the examined HNSCC samples had an immune cell phenotype similar to that seen in MEL. PD-L1 expression and the presence of tumor-infiltrating lymphocytes were strongly associated with the mesenchymal phenotype of HNSCC, suggesting a potential benefit for PD-1 blockade.[47] Indeed, several PD-1 and PD-L1 antibodies have induced impressive objective responses. Preliminary data on the antitumor activity of pembrolizumab from the HNSCC dose expansion cohort of the phase Ib KEYNOTE-012 trial were recently presented.[48] Patients had to have at least 1% PD-L1 expression in their tumor samples to participate. Sixty eligible patients were treated with pembrolizumab. At the time of data cutoff in May 2014, the best overall response rate was 19.6% (95% CI, 10.2–32.4). Both HPV-positive and HPV-negative patients responded in equal percentages. One patient had pseudoprogression followed by partial response on treatment. MEDI4736 has also demonstrated activity in metastatic HNSCC. At 10 mg/kg every 2 weeks, it showed an overall ORR of 14% (3/22), including 2 of 4 PD-L1-positive and 1 of 16 (6%)
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PD-L1-negative patients.[19] There was impressive shrinkage of a fungating mass of metastatic HNSCC following two doses of MEDI4736 in a 96-year-old woman. Similarly, Herbst et al reported on a patient with metastatic HNSCC with inflamed cutaneous lesions over the chest wall who had remarkable tumor regression after the first infusion and over the following course of MPDL3280A.[49] A phase III trial of pembrolizumab vs standard of care as second-line therapy is underway for metastatic recurrent HNSCC (NCT02252042).

Metastatic Colorectal Cancer and Gastric Carcinoma

An early report of a CR involved a patient with advanced metastatic CRC.[50,51] The patient was a 71-year-old man with microsatellite instability (MSI)-high metastatic CRC (mCRC), who developed metastatic disease 1 year after completion of adjuvant chemotherapy and who had received multiple lines of chemotherapies. He received a single dose of an anti-PD-1 antibody at 3 mg/kg in mid-2007. His first two restaging scans, obtained at 8 and 12 weeks after the dose, confirmed a partial response. He subsequently received additional doses, up to 5 over the following 9 months, and achieved a CR at 6 months. IHC studies of his primary tumor showed PD-L1 expression by infiltrating immune cells and by tumor cells, associated with infiltrating PD-1-positive, CD3+ T cells. Based on this observation and others, it has been hypothesized that MSI-high tumors with a high propensity for mutation would generate more neoantigens and make them more susceptible to immune recognition and attack. Llosa et al evaluated the immune tumor microenvironment of MSI-high and microsatellite-stable (MSS) CRC tumor samples.[52] The MSI-high specimens (n = 8) were characterized by higher infiltration of CD3+, CD4+, and CD8+ cells vs MSS samples (n = 7). Furthermore, the tumor microenvironment of MSI-high CRC was characterized by a high expression of IFN-gamma and genes associated with cytotoxic T cells, as well as greater expression of IFN-gamma-driven immune checkpoints, such as PD-1 and PD-L1.

Gatalica et al[53] reported that MSI-high tumors were significantly more frequently infiltrated by PD-1-positive intraepithelial lymphocytes than MSS tumors (72% vs 39%). Similarly, PD-L1-positive tumor cells were more common in MSI-high than in MSS samples (56% vs 21%; P = .007). Concurrent PD-1-positive intraepithelial lymphocytes and PD-L1 tumor cells were seen more frequently in MSI-high vs MSS samples (30% vs 5%; P = .008).

While few official data are available in this disease group, MPDL3280A reportedly has shown confirmed responses in mCRC and gastric carcinoma.[54] Currently, a phase II trial of nivolumab vs nivolumab plus ipilimumab is recruiting patients with recurrent and metastatic MSI-high colon cancer (NCT02060188), with a primary outcome measure of ORR. Another ongoing phase I study of nivolumab with or without ipilimumab is evaluating safety and antitumor activity in patients with pancreatic or gastric cancers (CA209-032).

Discussion

PD-L1 expression and patient selection

PD-1/PD-L1 pathway inhibitors have a high potential to impact cancer therapy. Although antitumor activity was seen more frequently in patients with positive PD-L1 expression status, activity in patients with unknown or “negative” status in multiple tumor types should not be discounted. There may be limitations to the use of PD-L1 as a predictive biomarker, for reasons that include the dynamic nature of the immune response and the change in immunologic phenotype over the course of a therapy.[55] Powderly et al demonstrated that PD-L1 expression is an adaptive change, and its expression status can change over time with anti-PD-L1 antibody therapy.[55] Thus, expression status determined from an archival tumor tissue may not reflect the tumor’s present immunologic phenotype. Another facet of this complex immune-mediated cytotoxicity is the role of tumor-infiltrating immune cells. At the end of the day, it is the immune cells in the tumor microenvironment that mediate cytotoxicity. Given the available data regarding PD-L1 status as a biomarker, clinical investigators have taken different approaches in selecting patients for larger phase II/III trials. For instance, whereas the pivotal trials of nivolumab (CheckMate 026) and pembrolizumab (KEYNOTE-024) for patients with untreated advanced NSCLC are enriched for patients with PD-L1-positive status, the phase III nivolumab trial in a second-line setting accepts all eligible patients regardless of PD-L1 status but randomizes them with their expression status as a stratification factor (CheckMate 057 and 017) (Table 7).

PD-1-targeted antibodies and autoimmune toxicities

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Immune checkpoint–targeted agents have given rise to a new spectrum of toxicity for clinicians to manage. Because of the role of the PD-L1/2-PD-1 axis in modulating the immune response under normal conditions, adverse events with potential immune-related causes would be expected. In the first published phase I report of nivolumab, drug-related adverse events of special interest (those with potential immune-related causes) were observed in 122/269 patients (44%), 18 (6%) > grade 3.[7] These events included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. Hepatic or gastrointestinal adverse events, predominantly diarrhea, were managed with treatment interruption and administration of glucocorticoids. These events were all reversible. Endocrine disorders were managed with replacement therapy. Drug-related pneumonitis occurred in nine patients (3%) and was grade 3/4 in three (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or number of doses was noted. Early-grade pneumonitis in six patients was reversible with treatment discontinuation, glucocorticoid administration, or both. In three patients with pneumonitis, infliximab, mycophenolate, or both were used for additional immunosuppression. Treatment with an anti-PD-1 antibody was reinitiated once the adverse event had been successfully managed, if the treating physician concurred. There were three drug-related deaths (1%) due to pneumonitis (two patients with NSCLC and one patient with CRC). Brahmer et al observed possible immune-related events of interest in 81 of 207 patients (39%); these included rash, hypothyroidism, hepatitis, and one case each of sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis in a trial of BMS936559 (anti-PD-L1 antibody).[17] These events were predominantly grade 1/2 and were managed with treatment interruption or discontinuation.

Mechanisms of resistance

Although anti-PD-1/PD-L1 antibodies have shown promising activity, benefits are limited to a fraction of patients. In other words, a significant percentage of patients have primary resistance to immune-checkpoint inhibitors.[2,56,57] Even after responses are achieved, a patient’s tumors will eventually acquire a resistance mechanism that will make it possible to re-escape the immune attack.

An observation of two major phenotypes of MEL metastases, “inflamed” and “noninflamed,” provides a good conceptual framework for understanding immune escape mechanisms. Inflamed tumors are characterized by tumor-infiltrating immune cells; noninflamed tumors are characterized by the lack thereof. While the tumor-infiltrating cytotoxic T lymphocyte is the key player in mediating cytotoxicity, in a tumor microenvironment there are multiple potential barriers to T-cell infiltration. These include, among others: (1) immune-suppressive cytokines (VEGF, interleukin [IL]-6, IL-8, etc), and (2) immune-suppressive cells (regulatory T cells, myeloid-derived suppressive cells, and tumor-associated macrophages). High levels of VEGF have been shown to delay dendritic cell migration and maturation, as well as adaptive immune response.[30] Additionally, the tumor cells themselves may also downregulate antigen presentation or costimulatory molecules, or upregulate additional immune checkpoint molecules to turn off activated T cells.

A biomarker biopsy study of the ongoing phase I study of MPDL3280A indicated that patients who responded to therapy had tumor-infiltrating lymphocytes and tumoral PD-L1 expression at baseline.[55] By contrast, in a PD-L1-negative patient not responding to therapy, very few CD8+ T cells were noted at the tumor periphery at baseline. Following therapy, there was minimal infiltration of T cells, and a gene expression study showed lack of cytotoxic T-cell marker expression.

Similar observations have been reported with anti–CTLA-4 antibodies,[58,59] implying that noninflamed tumors may have a greater tendency to be resistant to this class of therapy. Several combination approaches are currently under investigation to overcome this mechanism of resistance. A preclinical study demonstrated that PD-1 and CTLA-4 combination blockade expanded infiltrating cytotoxic T cells and reduced immune-suppressive cells.[20] This finding serves as a rationale for many ongoing clinical investigations. Dual blockade of CTLA-4 and PD-1 has resulted in dramatic clinical responses in MEL patients,[60] as well as in the other tumor types we have reviewed here.

Several other combination approaches using immune-modulatory agents, including IFN-alfa, IL-2, antiangiogenic agents, and tyrosine kinase inhibitors, are underway. Among these agents, colony-stimulating factor 1 receptor (CSF1R) inhibitor is of interest. Colony-stimulating factor is a chemokine that recruits tumor-infiltrating myeloid cells, such as M2 macrophages and myeloid-derived suppressor cells. In a preclinical study using a syngeneic mouse model of BRAF -driven MEL, inhibition of CSF1/CSF1R led to effective adoptive T-cell transfer by inhibiting intratumoral accumulation of immunosuppressive macrophages.[61] Another way to overcome this immune suppression is by adding an immune “accelerator,” such as...
immune-stimulatory agonistic immunoglobulins; OX40 (CD134), GITR, 4-1BB (CD137), and CD40 are in clinical development as monotherapies and in combination with immune checkpoint inhibitors.\[62\]

As an example, OX40 is a potent T-cell costimulatory receptor.\[63\] OX40 ligands are expressed on antigen-presenting cells. The engagement of OX40 by its ligand leads to enhanced T-cell survival, proliferation, effector function, and cytokine release, and inhibits regulatory T-cell function. An anti-OX40 monoclonal antibody (9B12) induced tumor regression in patients with MEL in a phase I study.\[64\]

**Perspective**

Cancer immunotherapy is entering a renaissance. Anti–PD-1/PD-L1 antibodies, in particular, have shown early but high promise in multiple tumor types. However, meticulous artistry in clinical trial design is essential to carve out the clinical benefits for carefully selected patients. The clinical benefits of this class of therapy may be expanded to a broader range of patients when “immunomodulatory” agents are shrewdly selected for combination studies. When this class of therapy becomes available to community oncologists, an algorithm will be implemented for treatment of immune-related adverse events. More importantly, heightened clinical acumen will be mandatory not only for detection of early signs of immune-mediated adverse events, but also for judicious use of corticosteroids to maximize clinical benefits.

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Table 5: Selected Trials for Non–Small-Cell Lung Cancer (NSCLC)

Table 6: Selected Trials for Other Tumor Types

References:


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