Toobey Lake Panorama_0104K (detail). Photograph courtesy of Henry Domke, MD. www.henrydomke.com

Anti–PD-1/PD-L1 agents have a good safety profile and have resulted in durable responses in a variety of cancers.

PD-1 Pathway Inhibitors: Changing the Landscape of Cancer Immunotherapy

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Background: *Immunotherapeutic approaches to treating cancer have been evaluated during the last few decades with limited success. An understanding of the checkpoint signaling pathway involving the programmed death 1 (PD-1) receptor and its ligands (PD-L1/2) has clarified the role of these approaches in tumor-induced immune suppression and has been a critical advancement in immunotherapeutic drug development.*
Methods: *A comprehensive literature review was performed to identify the available data on checkpoint inhibitors, with a focus on anti–PD-1 and anti–PD-L1 agents being tested in oncology. The search included Medline, PubMed, the ClinicalTrials.gov registry, and abstracts from the American Society of Clinical Oncology meetings through April 2014. The effectiveness and safety of the available anti–PD-1 and anti–PD-L1 drugs are reviewed.*
Results: *Tumors that express PD-L1 can often be aggressive and carry a poor prognosis. The anti–PD-1 and anti–PD-L1 agents have a good safety profile and have resulted in durable responses in a variety of cancers, including melanoma, kidney cancer, and lung cancer, even after stopping treatment. The scope of these agents is being evaluated in various other solid tumors and hematological malignancies, alone or in combination with other therapies, including other checkpoint inhibitors and targeted therapies, as well as cytotoxic chemotherapy.*
Conclusions: *The PD-1/PD-L1 pathway in cancer is implicated in tumors escaping immune destruction and is a promising therapeutic target. The development of anti–PD-1 and anti–PD-L1 agents marks a new era in the treatment of cancer with immunotherapies. Early clinical experience has shown encouraging activity of these agents in a variety of tumors, and further results are eagerly awaited from completed and ongoing studies.*

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Introduction

An intact immune system is capable of recognizing and eliminating tumor cells through immune checkpoints; however, tumors can adapt and circumvent these natural defense mechanisms.[1-3] Over the last several decades, significant efforts have targeted and activated the immune system to treat cancers; presently, increasing evidence exists that tumors can evade adaptive immunity and disrupt T-cell checkpoint pathways. The interaction between the programmed death 1 (PD-1) receptor and its ligand 1 and 2 (PD-L1/2) is a key pathway hijacked by tumors to

suppress immune control.[2,4-7] Reversing the inhibition of adaptive immunity can lead to active stimulation of a patient's immune systems; one such approach utilizes antagonistic antibodies to block checkpoint pathways, thus releasing tumor inhibition. These antagonistic antibodies target cytotoxic T-lymphocyte antigen 4 (CTLA-4), the PD-1 receptor and PD-L1, block immune checkpoints, and facilitate antitumor activity. These agents are unique among antagonistic antibodies because they target lymphocyte receptors or their ligands.[8,9]

In this review, we discuss the role of the PD-1/PD-L1 pathway and the drug development efforts to block this pathway in cancer, focusing on the currently available data from completed and ongoing clinical trials. The clinical development of several anti–PD-1 and anti–PDL-1 agents, their efficacy, toxicity, and scope in these cancers as single agents, or in combination with other therapies, will also be discussed.

Role of PD-1/PD-L1 Pathway

PD-1 is an immunoinhibitory receptor that belongs to the CD28 family and is expressed on T cells, B cells, monocytes, natural killer cells, and many tumor-infiltrating lymphocytes (TILs)[10]; it has 2 ligands that have been described (PD-L1 [B7H1] and PD-L2 [B7-DC]).[11] Although PD-L1 is expressed on resting T cells, B cells, dendritic cells, macrophages, vascular endothelial cells, and pancreatic islet cells, PD-L2 expression is seen on macrophages and dendritic cells alone.[10] Certain tumors have a higher expression of PD-L1.[12] PD-L1 and L2 inhibit T-cell proliferation, cytokine production, and cell adhesion.[13] PD-L2 controls immune T-cell activation in lymphoid organs, whereas PD-L1 appears to dampen T-cell function in peripheral tissues.[14] PD-1 induction on activated T cells occurs in response to PD-L1 or L2 engagement and limits effector T-cell activity in peripheral organs and tissues during inflammation, thus preventing autoimmunity. This is a crucial step to protect against tissue damage when the immune system is activated in response to infection.[15-17] Blocking this pathway in cancer can augment the antitumor immune response.[18] Like the CTLA-4, the PD-1 pathway down-modulates T-cell responses by regulating overlapping signaling proteins that are part of the immune checkpoint pathway; however, they function slightly differently.[14,16] Although the CTLA-4 focuses on regulating the activation of T cells, PD-1 regulates effector T-cell activity in peripheral tissues in response to infection or tumor progression.[16] High levels of CTLA-4 and PD-1 are expressed on regulatory T cells and these regulatory T cells and have been shown to have immune inhibitory activity; thus, they are important for maintaining self-tolerance.[16]

The role of the PD-1 pathway in the interaction of tumor cells with the host immune response and the PD-L1 tumor cell expression may provide the basis for enhancing immune response through a blockade of this pathway.[16] Drugs targeting the PD-1 pathway may provide antitumor immunity, especially in PD-L1 positive tumors. Various cancers, such as melanoma, hepatocellular carcinoma, glioblastoma, lung, kidney, breast, ovarian, pancreatic, and esophageal cancers, as well as hematological malignancies, have positive PD-L1 expression, and this expression has been correlated with poor prognosis.[8,19]

Melanoma and kidney cancer are prototypes of immunogenic tumors that have historically been known to respond to immunotherapeutic approaches with interferon alfa and interleukin 2. The CTLA-4 antibody ipilimumab is approved by the US Food and Drug Administration for use in melanoma. Clinical activity of drugs blocking the PD-1/PD-L1 pathway has been demonstrated in melanoma and kidney cancer.[20-24]

In patients with kidney cancer, tumor, TIL-associated PD-L1 expression, or both were associated with a 4.5-fold increased risk of mortality and lower cancer-specific survival rate, even after adjusting for stage, grade, and performance status.[18,19,25,26] A correlation between PD-L1 expression and tumor growth has been described in patients with melanoma, providing the rationale for using drugs that block the PD-1/PD-L1 pathway.[19,27]

Historically, immunotherapy has been ineffective in cases of non–small-cell lung cancer (NSCLC), which has been thought to be a type of nonimmunogenic cancer; nevertheless, lung cancer can evade the immune system through various complex mechanisms.[28] In patients with advanced lung cancer, the peripheral and tumor lymphocyte counts are decreased, while levels of regulatory T cells ($CD4^+$), which help suppress tumor immune surveillance, have been found at higher levels.[29-32] Immune checkpoint pathways involving the CTLA-4 or the PD-1/PD-L1 are involved in regulating T-cell responses, providing the rationale for blocking this pathway in NSCLC with antibodies against CTLA-4 and the PD-1/PD-L1 pathway.[32]

Triple negative breast cancer (TNBC) is an aggressive subset of breast cancer with limited treatment options. PD-L1 expression has been reported in patients with TNBC. When PD-L1 expression was evaluated in TILs, it correlated with higher grade and larger-sized tumors.[33] Tumor PD-L1 expression also correlates with the infiltration of T-regulatory cells in TNBC, findings that suggest the role of PD-L1–expressing tumors and the PD-1/PD-L1–expressing TILs in regulating immune response in TNBC.[34]

The PD-1/PD-L1 interaction may create an initial site for viral infection followed by an adaptive immune resistance, and PD-1 levels may positively correlate with a favorable outcome.[35,36] It is hypothesized that human papilloma virus (HPV)–associated oropharyn-

geal cancers express PD-L1 as an immune evasion mode and PD-L1–expressing tumors were more likely to be HPV positive, thus pointing to the potential role of this pathway as a therapeutic target in HPV-associated head and neck cancer. No correlation existed between PD-L1 expression and disease recurrence, but a correlation was seen between PD-L1 expression and the development of distant metastases.[37]

Drugs Targeting the PD-1 vs PD-L1 Pathway

The anti–PD-1 antibody blocks interactions between PD-1 and its ligands, PD-L1 and PD-L2, while the anti–PD-L1 antibody blocks interactions between PD-L1 and both PD-1 and B7-1 (CD80), which is implicated in the down-modulation of T-cell responses. Several PD-1 and PD-L1 inhibitors are in clinical development in early- and late-stage clinical trials across a wide variety of cancers (Tables 1 and 2).

Patterns and Evaluation of Response

A finding related to response to the anti–PD-1/PD-L1 drugs is that a flare response can be seen, with transient worsening of disease or its progression before stabilization or tumor regression occurs. Patients may exhibit durable responses, and, after discontinuing therapy, they may respond to re-treatment with these therapies in cases of progression.[23] From early clinical experience, both the anti–PD-1 and the anti–PD-L1 drugs appear to have activity in various cancers, but no definitive conclusions can be drawn regarding the differences in their effectiveness.[20-24,38-41] However, looking at available results from several studies, it appears that objective responses for anti–PD-L1 antibodies may be somewhat lower than those with anti–PD-1 antibodies, because the latter blocks signaling via both the PD-L1 and PD-L2.[20-24,38-41]

Safety

The anti–PD-1/PD-L1 agents are relatively well tolerated. However, drug-related adverse events with potential immune-related causes, such as pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis, can occur. The incidence of immune-related adverse events with anti–PD-1/PD-L1 agents is similar to that seen with ipilimumab but is less severe.[20-24,38-42] A comparison of immune-related adverse events with anti–PD-1/PD-L1 drugs, including ipilimumab, is shown in Table 3.[20,21,23,39,42] An often severe adverse event that has emerged with these agents is pneumonitis; high levels of PD-L1–expressing antigen-presenting cells seen in the lung may give relevance not only to the toxicity across cancers but also the observed responses in NSCLC.[43] Pneumonitis may be associated with anti–PD-1 drugs, not with anti–PD-L1 drugs, making the latter potentially safer.[20-24,38-42]

PD-L1 Inhibitors

BMS-936559/MDX-1105 is a fully human, high affinity, immunoglobulin (Ig) G4 monoclonal antibody to PD-L1. Initial results from a phase 1 trial of 207 patients

Table 1. — Selected Ongoing Clinical Trials of Anti–PD-L1 Drugs

Indication	Compound	Clinical Trials No.	Phase
Advanced solid tumors	BMS-936559	NCT00729664	1
	MEDI4736	NCT01693562	1
Melanoma	MPDL3280A + vemurafenib	NCT01656642	1b
	MEDI4736 + dabrafenib + trametinib or trametinib alone	NCT02027961	1/2
NSCLC	MPDL3280A + erlotinib	NCT02013219	1b
	MPDL3280A	NCT01846416	2
	MPDL3280A	NCT02031458	2
	MPDL3280A vs docetaxel	NCT01903993	2
	MPDL3280A vs docetaxel	NCT02008227	3
	MEDI4736 + tremelimumab	NCT02000947	1b
RCC	MPDL3280A ± bevacizumab vs sunitinib	NCT01984242	2
Solid or hematological malignancies	MPDL3280A	NCT01375842	1
Solid tumors	MPDL3280A + bevacizumab and/or chemotherapy	NCT01633970	1
	MPDL3280A + cobimetinib	NCT01988896	1
	MEDI4736	NCT01938612	1
	MEDI4736 + tremelimumab	NCT01975831	1
	MSB0010718C	NCT01943461	1
	MSB0010718C	NCT01772004	1

PD-L1 = programmed death ligand 1, NSCLC = non–small-cell lung cancer, RCC = renal cell carcinoma.

Table 2. — Ongoing Clinical Trials of Anti–PD-1 Drugs for Solid Tumors

Indication	Compound	Clinical Trials No.	Phase
Advanced cancer	AMP-224	NCT01352884	1
Advanced solid tumors	Nivolumab + iliolumbar (anti-KIR)	NCT01714739	1
Castration-resistant prostate cancer, melanoma, NSCLC, RCC	Nivolumab	NCT00730639	1b
Colon	Pembrolizumab	NCT01876511	2
Gastric, head and neck, TNBC, urothelial	Pembrolizumab	NCT01848834	1
Gastric, pancreatic, small-cell lung cancer, TNBC	Nivolumab ± ipilimumab	NCT01928394	1/2
Glioblastoma	Nivolumab ± ipilimumab vs bevacizumab	NCT02017717	2
Hepatocellular	Nivolumab	NCT01658878	1
Hodgkin lymphoma, myeloma, myelodysplastic syndrome, non-Hodgkin lymphoma	Pembrolizumab	NCT01953692	1
Malignant gliomas	Pidilizumab	NCT01952769	1/2
Melanoma	Nivolumab ± ipilimumab vs ipilimumab	NCT01844505	3
	Nivolumab + ipilimumab vs ipilimumab	NCT01927419	2
	Nivolumab + ipilimumab	NCT01024231	1
	Nivolumab sequentially with ipilimumab	NCT01783938	2
	Nivolumab vs DTIC or carboplatin/paclitaxel after ipilumumab	NCT01721746	3
	Nivolumab vs DTIC	NCT01721772	3
	Nivolumab + multiple class 1 peptides and montanide ISA 51 VG	NCT01176461	1
	Nivolumab + multiple class 1 peptides and montanide ISA 51 VG	NCT01176474	1
	Nivolumab	NCT01621490	1
	Pembrolizumab vs chemotherapy	NCT01704287	2
	Pembrolizumab vs ipilimumab	NCT01866319	3
Melanoma, NSCLC	Pembrolizumab	NCT01295827	1
NSCLC	Nivolumab ± gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab, erlotinib, ipilimumab	NCT01454102	1
	Nivolumab vs docetaxel	NCT01673867	3
	Nivolumab vs docetaxel	NCT01642004	3
	Nivolumab	NCT01721759	3
	Nivolumab	NCT01928576	2
	Pembrolizumab vs docetaxel	NCT01905657	2/3
	Pembrolizumab	NCT02007070	1
Pancreatic	Pidilizumab + gemcitabine	NCT01313416	2
Prostate	Pidilizumab + sipuleucel-T + cyclophosphamide	NCT01420965	2
RCC	Nivolumab + sunitinib, pazopanib, or ipilimumab	NCT01472081	1
	Nivolumab	NCT01354431	2
	Nivolumab vs everolimus	NCT01668784	2
	Nivolumab	NCT01358721	1
	Pembrolizumab + pazopanib	NCT02014636	1
	Pidilizumab ± dendritic cell/RCC fusion cell vaccine	NCT01441765	2
Solid tumors	Anti-LAG3 (BMS-986016) ± nivolumab	NCT01968109	1
	Nivolumab	NCT00836888	1
	Nivolumab + interleukin-21	NCT01629758	1
	AMP-554	NCT02013804	1
Solid tumors, NSCLC	Pembrolizumab	NCT01840579	1

PD-1 = programmed death 1, NSCLC = non–small-cell lung cancer, RCC = renal cell carcinoma, TNBC = triple negative breast cancer.

showed durable tumor regression (objective response rate of 6%–17%) and prolonged stabilization of disease (12%–41% at 24 weeks) in patients with advanced cancers, including NSCLC, melanoma, and kidney cancer.[20]

MPDL3280A is an engineered human monoclonal antibody targeting PD-L1. In a phase 1 study of 171 patients with advanced solid tumors, an overall response rate of 21% was observed in nonselected solid tumors among several patients exhibiting delayed responses following initial radiological progression.[39] The 24-week progression free survival rate was 44%. Patients with PD-L1 expressing tumors had an overall response rate of 39% and 12% had progressive disease. Those with PD-L1 tumors had an overall response rate of 13% and 59% had progressive disease.[39]

Additional anti–PD-L1 agents, including MSB0010718C and MEDI473, are being tested in early-phase trials (see Table 1).

PD-1 Inhibitors

CT-011/pidilizumab is a humanized IgG1 monoclonal antibody that binds to PD-1. A phase 1 study in 17 patients with advanced stage hematologic malignancies (acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin lymphoma, multiple myeloma, non-Hodgkin lymphoma) showed a clinical benefit in 33% patients and a prolonged complete response of longer than 68 weeks in 1 patient.[38] Several phase 1 and 2 trials are ongoing to study the use of this agent in various solid tumors, including prostate and renal cell cancers (see Table 2).

BMS-936558/MDX-1106/nivolumab is a fully human IgG4 monoclonal antibody against PD-1. The first human study evaluated its safety and tolerability in 39 patients with advanced refractory solid tumors.[22] Results of a larger phase 1 study in 296 patients have also been reported.[23,24,40] Objective responses were seen in 31% of patients with melanoma, 17% in patients with NSCLC, and 29% in patients with RCC.[40] A total of 65% of responders had durable responses lasting for more than 1 year. Stable disease lasting 24 weeks was seen in patients with melanoma (7%), NSCLC (10%), and RCC (27%). The median overall survival rate for patients with melanoma was 16.8 months. PD-L1 expression was tested in 42 patients; 9 out of 25 (36%) patients had PD-L1–expressing tumors and experienced an objective response to PD-1 blockade, while the remaining 17 patients had PD-L1–negative tumors that were nonresponsive.[23]

Pembrolizumab is a highly selective, humanized IgG4-kappa monoclonal antibody with activity against PD-1. Its safety and efficacy were evaluated in a phase 1 trial in solid tumors.[41] The rate of median progression-free survival was more than 7 months; however, the median overall survival rate was not been reached.

Rationale for Combination Therapies

Thus far, anti–PD1 and anti–PD-L1 antibodies have yielded promising results with durable responses in several tumors and a reasonable safety profile. Given that these agents produce durable responses despite treatment discontinuation, it is thought that the

Table 3. — Comparison of Immune-Related Adverse Events Between Anti–PD-1/PD-L1 Drugs and Ipilimumab

	Ipilimumab (%)[42]	Nivolumab/ BMS-936558 (%)[23]	Pembrolizumab/ MK-3475 (%)[21]	Pidilizumab/ CT-011 (%)[35]	BMS-936559 (%)[20]	MPDL3280A (%)[39]
Colitis	7.6/5.3	14	13	0	9	39
Dermatological	43/1.5	23	21/2			
Diarrhea	33/5	18	20/1			
Fatigue	42/7	32	30/1			
Hepatic			13/1			
Hypothyroid			8/1			
Hypophysitis	1.5/1.5					
Infusion reactions					10	
Pneumonitis		/1	4/0			0/0
Pruritus			21			
Total grade 3/4	**45.8**					
Total immune-related	**96.9**	**0**	**79**	**61**	**39**	**0**

PD = programmed death 1, PD-L1 = programmed death ligand 1, NSCLC = non–small-cell lung cancer, RCC = renal cell carcinoma.

re-education of the immune system helps it adapt to tumor manipulation to develop resistance.[16]

Preclinical evidence exists for the complementary roles of CTLA-4 and PD-1 in regulating adaptive immunity, and this provides rationale for combining drugs targeting these pathways.[44-46] Paradoxically and originally believed to be immunosuppressive, new data allow us to recognize that cytotoxic agents can antagonize immunosuppression in the tumor microenvironment, thus promoting immunity based on the concept that tumor cells die in multiple ways and that some forms of apoptosis may lead to an enhanced immune response.[8,15] For example, nivolumab was combined with ipilimumab in a phase 1 trial of patients with advanced melanoma.[46] The combination had a manageable safety profile and produced clinical activity in the majority of patients, with rapid and deep tumor regression seen in a large proportion of patients. Based on the results of this study, a phase 3 study is being undertaken to evaluate whether this combination is better than nivolumab alone in melanoma (NCT01844505). Several other early-phase studies are underway to explore combinations of various anti–PD-1/PD-L1 drugs with other therapies across a variety of tumor types (see Tables 1 and 2), possibly paving the way for future combination studies.

PD-L1 as a Predictive Biomarker

Tumor PD-L1 expression has been shown to correlate with poor prognosis in many cancers.[47] Available early data allude to PD-L1 expression in tumors as a possible predictive biomarker of response to anti–PD-1/PD-L1 drugs; however, these data must be confirmed, and the role of tumor expression of PD-L1 must be further elucidated.

Conclusions

The discovery of agents targeted at the anti–programmed death 1 and anti–programmed death ligand 1 pathway, as well as their remarkable activity in several cancers, has launched an era of effective immunotherapeutic drugs that will change the landscape of cancer treatment. These agents also produce responses in nonimmunogenic cancers such as non–small-cell lung and colon cancers, broadening their scope beyond classic immunogenic tumors like melanoma and renal cell cancer.[20] The activity of these agents has been suggested in early-phase studies of melanoma, renal cell, and non–small-cell lung cancers, and the results from completed and ongoing phase 3 studies are eagerly awaited. In addition, these agents are being explored alone or in combination across other difficult-to-treat tumor types.

In summary, the programmed death 1/programmed death ligand 1 pathway inhibitors have made an addition to the armamentarium of currently available immunotherapeutic drugs and carry great potential for treating immunogenic as well as nonimmunogenic cancers.

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