REVIEW ARTICLE

Immune Checkpoint Blockade in Cancer Therapy

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ABSTRACT

Immunologic checkpoint blockade with antibodies that target cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1) have demonstrated promise in a variety of malignancies. Ipilimumab (CTLA-4) and pembrolizumab (PD-1) are approved by the US Food and Drug Administration for the treatment of advanced melanoma, and additional regulatory approvals are expected across the oncologic spectrum for a variety of other agents that target these pathways. Treatment with both CTLA-4 and PD-1/PD-L1 blockade is associated with a unique pattern of adverse events called immune-related adverse events, and occasionally, unusual kinetics of tumor response are seen. Combination approaches involving CTLA-4 and PD-1/PD-L1 blockade are being investigated to determine whether they enhance the efficacy of either approach alone. Principles learned during the development of CTLA-4 and PD-1/PD-L1 approaches will likely be used as new immunologic checkpoint blocking antibodies begin clinical investigation.

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INTRODUCTION

The immune system plays an important role in controlling and eradicating cancer. Nevertheless, in the setting of malignancy, multiple mechanisms of immune suppression may exist that prevent effective antitumor immunity. Antibody therapy directed against several negative immunologic regulators (checkpoints) is demonstrating significant success and is likely to be a major component of treatment for patients with a variety of malignancies.

This review is focused on antibodies that block cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1). We discuss the preclinical rationale and clinical experience with these antibodies and then review the unique considerations relevant for treating patients with these agents.

CTLA-4 PRECLINICAL RATIONALE AND CLINICAL EFFICACY

CTLA-4 was the first immune checkpoint receptor to be clinically targeted (Fig 1) Normally, after T-cell activation, CTLA-4 is upregulated on the plasma membrane where it functions to downregulate T-cell function through a variety of mechanisms, including preventing costimulation by outcompeting CD28 for its ligand, B7, and also by inducing T-cell cycle arrest.[1-5] Through these mechanisms and others, CTLA-4 has an essential role in main-

taining normal immunologic homeostasis, as evidenced by the fact that mice deficient in CTLA-4 die from fatal lymphoproliferation.[6,7] Recognizing the role of CTLA-4 as a negative regulator of immunity, investigators led studies demonstrating that antibody blockade of CTLA-4 could result in antitumor immunity in preclinical models.[8,9]

On the basis of this preclinical rationale, two antibodies targeting CTLA-4, ipilimumab (Bristol-Myers Squibb, Princeton, NJ) and tremelimumab (formerly Pfizer, currently MedImmune/AstraZeneca, Wilmington, DE), entered clinical development. Early reports of both agents showed durable clinical responses in some patients.[10-12] Unfortunately, despite a proportion of patients experiencing a durable response, tremelimumab did not statistically significantly improve overall survival, which led to a negative phase III study comparing tremelimumab to dacarbazine/temozolomide in patients with advanced melanoma.[13] It is possible that the lack of an overall survival benefit was a result of the crossover of patients treated with chemotherapy to an expanded access ipilimumab program or a result of the dosing or scheduling considerations of tremelimumab.

Ipilimumab, however, was successful in improving overall survival in two phase III studies involving patients with advanced melanoma.[14,15] Although the median overall survival was only improved by several months in each of these studies, landmark survival after treatment initiation favored ipilimumab; in the first phase III study, 18% of patients were alive after 2 years compared with 5% of
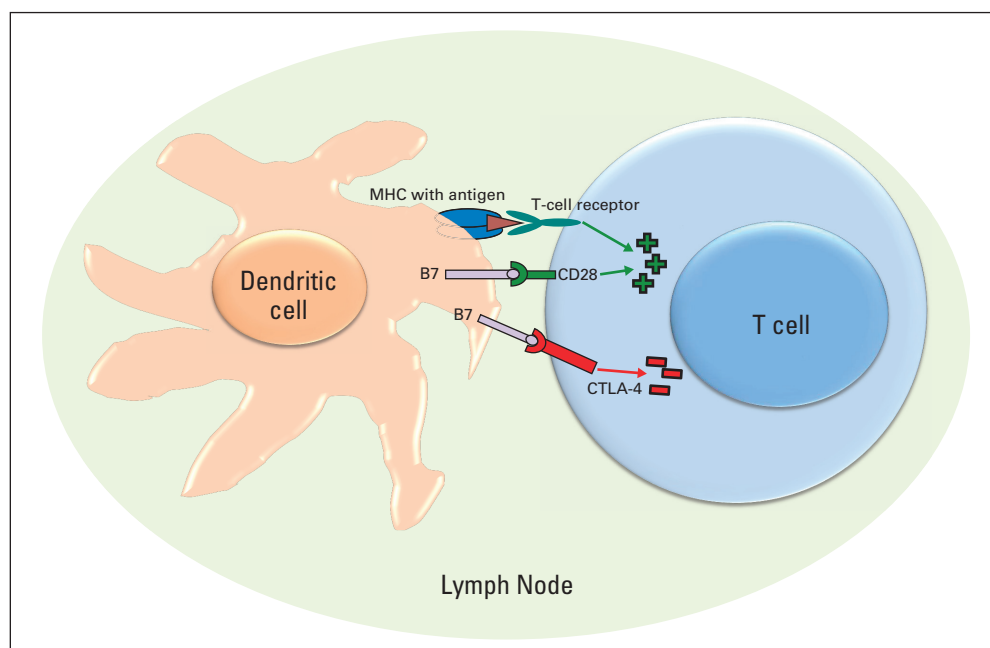
Fig 1. The cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic checkpoint. T-cell activation requires antigen presentation in the context of a major histocompatibility complex (MHC) molecule in addition to the costimulatory signal achieved when B7 on an antigen-presenting cell (dendritic cell shown) interacts with CD28 on a T cell. Early after activation, to maintain immunologic homeostasis, CTLA-4 is translocated to the plasma membrane where it downregulates the function of T cells.

patients who received the control treatment of gp100 vaccination.[14] More recently reported pooled data from clinical trials of ipilimumab confirm that approximately 20% of patients will have long-term survival of at least 3 years after ipilimumab therapy, with the longest reported survival reaching 10 years.[16-18]

For patients with other malignancies, CTLA-4 antibody therapy has also shown some benefits. Ipilimumab, in combination with carboplatin and paclitaxel in a phased treatment schedule, showed improved progression-free survival compared with carboplatin and paclitaxel alone for patients with non–small-cell lung cancer.[19] Several patients with pancreatic cancer had declines in CA 19-9 when ipilimumab was given with GVAX (Aduro, Berkeley, CA),[20] and ipilimumab has also resulted in responses in patients with prostate cancer.[21] Unfortunately, a phase III study in patients with castrate-resistant prostate cancer who experienced progression on docetaxel chemotherapy demonstrated that after radiotherapy, ipilimumab did not improve overall survival compared with placebo.[22] Although this study is felt to have been a negative study, ipilimumab may have conferred a benefit to patients with favorable prognostic features, such as the absence of visceral metastases, but this requires further study. Another CTLA-4–blocking antibody, tremelimumab, has shown responses in patients with mesothelioma, and ongoing trials are under way.[23]

PD-1 PRECLINICAL RATIONALE AND CLINICAL EFFICACY

Success targeting CTLA-4 has created enthusiasm for clinical approaches targeting other immunologic checkpoints, namely PD-1/PD-L1 (Fig 2). PD-1 is a negative regulator of T-cell activity that limits the activity of T cells at a variety of stages of the immune response when it interacts with its two ligands PD-L1 and PD-L2.[24-26] When engaged by ligand, through phosphatase activity, PD-1 inhibits kinase signaling pathways that normally lead to T-cell activation.[25] Mice deficient in PD-1 have a distinct autoimmune phenotype from

mice deficient in CTLA-4.[27,28] Perhaps this finding is unsurprising because, unlike CTLA-4, which is primarily believed to regulate immune responses early in T-cell activation, PD-1 is primarily believed to inhibit effector T-cell activity in the effector phase within tissue and tumors.[29] PD-1 is expressed on many immunologic cells, including B cells and natural killer cells, and therapeutic blockade of the PD-1 pathway may influence the function of these cells as well.[29,30]

A number of antibodies that disrupt the PD-1 axis have entered clinical development. Although the various antibodies differ in structure (Table 1), they can largely be broken down into the following two main categories: those that target PD-1 (nivolumab, Bristol-Myers Squibb; pembrolizumab, Merck, Whitehouse Station, NJ; pidilizumab, CureTech, Yavne, Israel) and those that target PD-L1 (MPDL3280A, Genentech, South San Francisco, CA; MEDI4736, MedImmune/AstraZeneca; BMS-936559, Bristol-Myers Squibb; MSB0010718C, EMD Serono, Rockland, MA). AMP-224 (Amplimmune, Gaithersburg, MD/GlaxoSmithKline, Philadelphia, PA) is a PD-L2 fusion protein that does not directly target PD-1 or PD-L1, but instead is believed to deplete PD-1–positive T cells.[31]

Both nivolumab and pembrolizumab have demonstrated highly durable response rates with minimal toxicity in large phase I studies involving patients with advanced melanoma, non–small-cell lung cancer, renal cell carcinoma, and other solid tumors.[32-34] Although initial enthusiasm for PD-1 blockade was generated from large phase I studies, randomized phase III data in patients with melanoma are now emerging. In one study of patients with melanoma who had experienced progression on ipilimumab, nivolumab resulted in a 32% overall response rate compared with 11% for chemotherapy (dacarbazine or carboplatin/paclitaxel) with less frequent high-grade treatment-related adverse events.[35] A separate phase III study testing nivolumab against dacarbazine chemotherapy in patients with advanced melanoma was stopped early by an independent data monitoring committee because patients treated with nivolumab had improved overall survival compared with patients treated with dacarbazine.
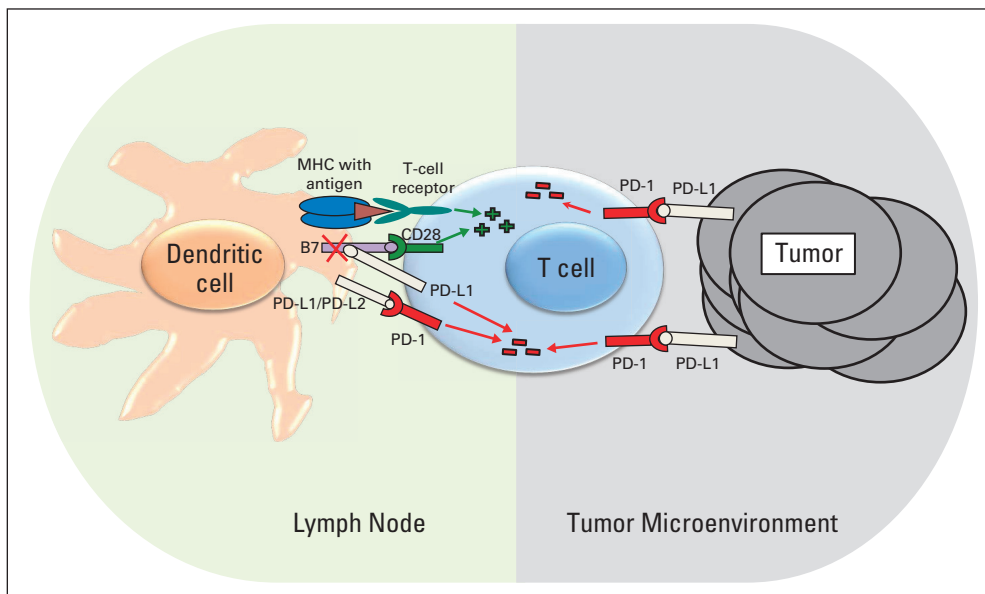
Fig 2. The programmed cell death protein 1 (PD-1) immunologic checkpoint. PD-1 is expressed on activated T cells. Interactions between PD-1 and its ligands, PD-L1 and PD-L2, are complex and occur at multiple steps of an immune response. For illustration, we have shown an interaction early after activation in the lymph node where PD-L1/PD-L2 on an antigen-presenting cell (dendritic cell shown) negatively regulates T-cell activity through PD-1 and through an interaction between B7 and PD-L1. The PD-1 pathway is also likely important in the tumor microenvironment where PD-L1 expressed by tumors interacts with PD-1 on T cells to suppress T-cell effector function. MHC, major histocompatibility complex.

Pembrolizumab has similarly been shown to result in impressive tumor responses and was recently approved by the US Food and Drug Administration for patients with melanoma previously treated with ipilimumab and, if relevant, a BRAF inhibitor.[36] Although nivolumab and pembrolizumab have predominantly demonstrated activity in solid tumors, pidilizumab has mostly been clinically evaluated in hematologic malignancies, with responses seen as monotherapy and in combination regimens with rituximab.[37-39]

Targeting PD-L1 is a similarly promising approach to targeting PD-1. Targeting PD-L1, however, may result in different biologic effects than targeting PD-1. In addition to binding PD-1, PD-L1 also is believed to exert negative signals on T cells by interacting with B7.[40] PD-L1–blocking antibodies prevent this interaction, but PD-1–blocking antibodies do not. Another slight difference is that PD-L1 antibodies do not prevent PD-1 from interacting with PD-L2, although the effect of this interaction remains unknown.

BMS-956559 was the first PD-L1 antibody to show objective tumor responses in patients with a variety of solid tumors.[41]

Table 1. PD-1 and PD-L1 Antibodies in Clinical Development

Target and Agent	Class
PD-1	
Nivolumab (MDX1106, BMS-936558)	IgG4 fully human Ab
Pembrolizumab (MK-3475)	IgG4 engineered humanized Ab
Pidilizumab (CT-011)	IgG1 humanized Ab
PD-L1	
BMS935559 (MDX-1105)	IgG4 fully human Ab
MPDL3280A	IgG1 engineered fully human Ab
MEDI4736	IgG1 engineered fully human Ab
MSB0010718C	IgG1 fully human Ab
PD-1–positive T cells	
AMP-224	Fc of human IgG–PD-L2 fusion

Abbreviations: Ab, antibody; IgG, immunoglobulin G; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein 1 ligand.

MPDL3280A, MEDI4736, and MSB0010718C have also been shown to result in disease responses in early-phase clinical trials in a number of malignancies including tumor types such as bladder cancer, head and neck cancer, and GI malignancies.[42-45]

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CLINICAL CONSIDERATIONS OF IMMUNE CHECKPOINT BLOCKADE

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Starting with the development of CTLA-4–blocking antibodies, several unique clinical considerations became apparent. The experience with PD-1/PD-L1 checkpoint blockade is less mature, but similar themes continue to emerge.

Patterns of Disease Response: The Immune-Related Response Criteria

Several patients treated in early studies with CTLA-4 blockade were noted to have early evidence of disease progression but ultimately achieved disease response.[46] In a report of some of the first patients treated with CTLA-4 blockade, the median time it took to achieve response for patients who achieved an ultimate complete response was 30 months.[17] In one long-term analysis of patients with melanoma who lived at least 4 years after ipilimumab, approximately 25% had never achieved an outcome better than progressive disease, as traditionally defined by WHO criteria.[16]

In an effort to capture possibly beneficial effects of CTLA-4 therapy beyond those captured by standard radiographic response criteria such as RECIST, investigators proposed alternative response criteria for immunologic checkpoint blockade called the immune-related response criteria (irRC).[47,48] In concept, the irRC enable new lesions to be included in the total tumor burden assessment without immediately being considered progressive disease and require confirmation of apparent initial disease progression on a subsequent radiographic assessment (Table 2). In a retrospective study of patients treated with ipilimumab in pooled phase II studies, the irRC were found to correlate with overall survival better than the traditional

Table 2. Differences Between RECIST (version 1.1) and irRC

Factor	RECIST	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Complete response	Disappearance of all target and nontarget lesions; lymph nodes must regress to < 10-mm short axis; no new lesions; requires confirmation	Same as for RECIST
Partial response	≥ 30% decrease in tumor burden compared with baseline; requires confirmation	≥ 50% decrease in tumor burden compared with baseline; requires confirmation
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir; progression of nontarget lesions and/or appearance of new lesions (at any single time point)	≥ 25% increase in tumor burden compared with most recent prior evaluation; new lesions added to tumor burden; requires confirmation
Stable disease	Any response pattern that does not meet criteria for complete response, partial response, or progressive disease	Same as for RECIST

Abbreviation: irRC, immune-related response criteria.

WHO response criteria.[47] The irRC developed from experience with CTLA-4 therapy, but some patients treated with PD-1 agents have similarly shown immune-related patterns of response.[32,33]

Although these atypical late responses can be seen, they are the exception. In one study of 192 patients treated with pembrolizumab, approximately 10% of patients with progressive disease by irRC at week 12 subsequently achieved some benefit from pembrolizumab therapy as either a response or stable disease.[49] In a recently presented phase III study of nivolumab versus chemotherapy, of 120 patients who received nivolumab, 10 (8%) had irRC responses.[35] This emerging experience with PD-1 atypical responses seems roughly similar to the ipilimumab experience. In pooled phase II data from 123 patients with progression on ipilimumab at the week 12 scan, five patients (4%) ultimately had an immune-related partial response, and 17 patients (14%) ultimately achieved stable disease.[47]

The irRC continue to be refined. Because efficacy to PD-1/PD-L1 checkpoint–blocking antibodies is typically made using the unidimensional RECIST criteria, a unidimensional irRC has been proposed.[50] Ultimately, the role of the irRC as a surrogate end point for efficacy of immune checkpoint blockade will depend on its eventual validation in ongoing randomized controlled prospective trials. If this prospective validation is attained, it will help solidify irRC as a clinical end point acceptable to regulatory authorities.

Immune-Related Adverse Events

Although immune checkpoint blockade can induce significant antitumor benefits, because checkpoint blockade does not just enhance tumor-specific immune responses, unique adverse effects can occur through nonspecific immunologic activation. Adverse effects from these agents have been termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. For clarity and simplicity throughout this review, we denote them all as irAEs. Although irAEs are different in character from adverse events caused by traditional chemotherapy or targeted therapy, the rate of grade 3 or 4 toxicity with immune checkpoint blockade (approximately 10% to 20%) is no greater than that seen with many standard chemotherapy or targeted therapy regimens.[51,52]

IrAEs include dermatologic, GI, hepatic, endocrine, and other less common inflammatory events. Because irAEs likely arise from general immunologic enhancement, temporary immunosuppression with corticosteroids, tumor necrosis factor α antagonists, mycophenolate mofetil, or other agents is often necessary and should follow established algorithms.[53] Recommendations for treating irAEs come from general clinical consensus because no prospective trials have been conducted to specifically test whether one management strategy is superior. Early recognition and treatment are believed to be important in mitigating severity.

The most common irAE for both CTLA-4 and PD-1 therapy involves dermatologic toxicity, which is also typically the irAE with the earliest onset, within several weeks (as reviewed for CTLA-4 by Weber et al[54]). Physical examination findings can consist of a reticular, maculopapular, erythematous rash on the extremities or trunk.[55] Perhaps more unique to the PD-1 experience, oral mucositis and/or complaints of dry mouth have been reported in a small percentage of patients.[34] Treatment for most rashes is successful with topical corticosteroids and antipruritics (eg, hydroxyzine, diphenhydramine), and oral corticosteroid rinses and lidocaine have anecdotally been effective in patients with mucositis. More rarely, severe rashes such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, and if suspected, hospitalization for intravenous corticosteroids, fluid, and electrolyte monitoring is required.

Perhaps the most clinically relevant irAE consists of diarrhea/colitis, which typically does not present until approximately 6 weeks into treatment after several doses of CTLA-4 blockade.[56] The incidence of grade 3 or 4 diarrhea with ipilimumab 3 mg/kg has been reported to be approximately 10%, but unfortunately, this adverse event has also resulted in treatment-related deaths.[14] Treatment of moderate symptoms should consist of oral corticosteroids. Hospitalization should be considered for intravenous corticosteroids if symptoms are severe or refractory to oral corticosteroids. Infliximab (5 mg/kg once every 2 weeks) can be helpful in corticosteroid-refractory patients.[57,58] The incidence of grade 3 or 4 diarrhea/colitis with PD-1 agents (approximately 1% to 2%)[32,33] is believed to be much lower than with CTLA-4 agents. Clostridium difficile and other infectious etiologies should be excluded.

Elevations in serum levels of hepatic enzymes (AST and ALT) can be seen with both CTLA-4 and PD-1 blockade, and in almost all cases, these are asymptomatic laboratory abnormalities only. With CTLA-4 blockade, grade 3 or 4 transaminitis is believed to occur less than 10% of the time,[13,14] and grade 3 or 4 transaminitis with PD-1 blockade is rare.[32,33] Patients should be managed with oral corticosteroids or, if refractory, mycophenolate mofetil (500 mg twice daily). Infliximab should not be used because it may contribute to hepatotoxicity.

Immune checkpoint blockade may also result in endocrinopathies affecting the pituitary, adrenal, and thyroid glands. Clinical symptoms may vary but often involve nonspecific symptoms such as fatigue, headache, and nausea. Diagnosis is usually made by characteristic laboratory findings and/or radiographic changes, such as enlargement of the pituitary gland.[59,60] Because the pituitary gland also regulates the ovary/testes, pituitary dysfunction may contribute to gonadal dysfunction in women and men of any age. The precise incidence of endocrinopathy is difficult to ascertain because endocrinopathies have been variably monitored and diagnosed in clinical trials. Treatment, as with other irAEs, consists of corticosteroids and, if needed, longer term hormone supplementation such as with levothyroxine or replacement hydrocortisone. Other rare irAEs, such as uveitis,[61] neurologic adverse effects,[62] pancreatitis,[63] hematologic adverse effects,[64,65] nephritis,[66] and pneumonitis,[32] have been described with checkpoint blockade. Pneumonitis is notable because rare treatment-related deaths have been experienced in early clinical studies of PD-1 blockade.[32]

Prolonged immunosuppression, often required to treat irAEs, unfortunately carries the risk of predisposing patients to opportunistic infections. In one case report, a patient treated with ipilimumab who required corticosteroids and infliximab for colitis ultimately developed *Aspergillus* pneumonia.[67] Given this risk, in patients receiving prolonged immunosuppression to treat an irAE, such as prednisone $\geq$ 20 mg per day for at least 4 weeks, we recommend considering prophylaxis against infectious organisms such as *Pneumocystis jirovecii* following the guidelines established by the National Comprehensive Cancer Network.[68]

Whether irAEs or other exacerbations of autoimmunity occur at a higher rate among patients with underlying autoimmune disorders is unknown because patients with autoimmune disorders were not included in clinical trials of CTLA-4 and PD-1/PD-L1 agents. Nonetheless, several cases have recently been reported of patients with autoimmune disorders successfully being treated with ipilimumab without exacerbation of their underlying autoimmune disorder.[69,70] Another study, however, indicated that a patient with multiple sclerosis had worsening symptoms after ipilimumab.[71] Clinicians contemplating this treatment in this patient population should weigh the potential benefits of CTLA-4 and PD-1/PD-L1 therapy in treating life-threatening malignancy against the theoretical risk of exacerbating an underlying autoimmune disorder.

ONGOING QUESTIONS

Optimizing Dose and Schedule

Many questions remain about the optimal dose and schedule of administering immunologic checkpoint blockade. In one phase II dose-finding study of ipilimumab, ipilimumab at 10 mg/kg compared with 3 mg/kg was associated with a numerically small but statistically significant higher response rate (11.1% v 4.2%, respectively; P = .0015) but similar rates of disease control. An ongoing randomized study powered for overall survival evaluating ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg will more definitively answer this question.

Across all PD-1 agents, multiple studies have shown that doses of PD-1 agents greater than 1 mg/kg do not increase efficacy. The largest experience evaluating dosing of a PD-1 antibody was a study of 173 patients with melanoma who were randomly assigned to pembrolizumab 10 mg/kg or 2 mg/kg administered every 3 weeks.[36] Efficacy and safety in both treatment arms were the same. Ongoing phase III studies of pembrolizumab and other PD-1 agents will continue to clarify whether there is a dose-response relationship with PD-1 agents.

The optimal scheduling of CTLA-4 and PD-1 antibodies is also not yet known. As per US Food and Drug Administration approval, ipilimumab is delivered every 3 weeks for four total treatments, called induction. In the large registrational ipilimumab study, patients who initially achieved stable disease or a response with acceptable toxicity but who subsequently experienced progression were offered a reinduction course of four additional doses of ipilimumab, with each dose administered 3 weeks apart.[14] Among the 31 patients who were treated with reinduction ipilimumab in this study, six patients (19%) achieved a subsequent complete or partial response with no new types of toxicities.[72] Retreating patients with ipilimumab who experienced some benefit from their initial ipilimumab course with minimal adverse effects is justified.

PD-1/PD-L1 antibodies are administered on a continuous schedule, yet it remains unclear as to whether this continuous dosing is necessary. Many published trials have shown that patients can have persistent responses lasting beyond the cessation of PD-1 therapy.[34] One patient who had benefit from nivolumab but who later experienced progression reinitiated nivolumab and later regained a response,[73] similar to the benefits seen in some patients who have received reinduction ipilimumab.

Biomarkers Associated With Disease Outcome

Treatment with immunologic checkpoint blockade would ideally be matched to patients who are most likely to benefit and least likely to experience adverse effects. The efficacy of CTLA-4 and PD-1 blockade also somewhat varies among different tumor types, and better understanding these differences would enhance the efficacy of this treatment modality. At this time, no single immunologic or tumoral characteristic in a patient has been found to solely determine response to an immunotherapeutic agent.

Both host immunologic and intratumoral factors have been examined with CTLA-4 blockade. In the peripheral blood, CTLA-4 blockade has been shown to result in T-cell activation and proliferation and an increase in antigen-specific immunity.[74-76] The absolute lymphocyte count has been found to be a specific pharmacodynamic biomarker of ipilimumab,[77] and the degree of increase in the absolute lymphocyte count has been associated with overall survival in patients with melanoma.[77-79] The activation marker, inducible costimulator, has also been found to increase during ipilimumab and correlate with benefit.[80,81] It is possible that these pharmacodynamic biomarkers may ultimately help refine early surrogate assessments of CTLA-4 efficacy and distinguish patient populations for subsequent clinical trials. Intratumorally, a high number of T regulatory cells, the presence of the immunosuppressive enzyme indoleamine 2,3-dioxygenase, and immune-active genetic profile have been associated with benefit from ipilimumab.[82,83] More recently, whole-exome sequencing of tumors from patients treated with CTLA-4 blockade has revealed mutations that lead to neoantigens, which may be immunologically relevant in responses to immune checkpoint blockade.[84,85]

Although PD-1/PD-L1 plays a role in inhibiting multiple stages of the immune response, PD-1/PD-L1 blockade is believed to be most relevant in the final stages of the immune response between a T cell

and tumor. Thus, most biomarker investigations for PD-1/PD-L1 agents have focused on the tumor microenvironment and, specifically, immunohistochemical expression of one of the ligands for PD-1, PD-L1. Across all studies in multiple tumor types, it seems that patients whose tumors express PD-L1, as detected by immunohistochemical assays, have numerically higher response rates to PD-1/PD-L1 blockade than patients who do not express PD-L1.[32,86,87] Nevertheless, patients who do not express PD-L1 can still have impressive responses to PD-1 blockade and should be considered eligible for PD-1–blocking approaches. It remains unclear whether differential expression levels of PD-L1 among various tumor types account for the somewhat different response rates observed. Yet, the explanation for the varying response rates to PD-1 blockade among different tumor types is likely more complex. PD-L1 is inducible and can be upregulated in response to infiltrating immune cells and, possibly, genetic changes within the tumor.[88-90] Technical considerations of PD-L1 assessments, such as the degree of staining required to be considered positive and whether staining the tumor cells or infiltrating immune cells is relevant, are areas of ongoing research. Until additional knowledge is attained, we do not support using PD-L1 to select patients for PD-1 blockade.

Combination Approaches

To improve on the number of patients who benefit from immune checkpoint blockade, CTLA-4 and PD-1/PD-L1 antibodies are being combined together and with other anticancer agents such as chemotherapy, targeted therapy, radiotherapy, and other immunotherapy. Many of these combination approaches are built on a robust scientific background, but data from randomized studies are not yet available to suggest that any specific combination approach is more efficacious than single-agent CTLA-4 or PD-1/PD-L1 blockade.

Although traditionally considered immunosuppressive, several preclinical studies indicate that chemotherapy may have immunostimulatory properties, as reviewed by Zitvogel et al.[91] Some trials in patients with non–small-cell lung cancer and melanoma showed that combinations of chemotherapy with ipilimumab were generally safe,[19,92] but others have reported an increase in specific adverse effects such as transaminitis.[15] Dose and schedule may be important in future trials to minimize toxicity and determine whether chemotherapy enhances or inhibits immune checkpoint blockade.

Targeted therapy directed at oncogenic signaling pathways, such as the *BRAF* mutation in melanoma, is also an attractive partner to combine with immune checkpoint blockade based on preclinical data, as reviewed by Hu-Lieskovan et al.[93] The combination of ipilimumab and vemurafenib resulted in frequent transaminitis in a phase I study and is not clinically recommended.[94] The combination of ipilimumab, dabrafenib, and trametinib also was found to be problematic, with frequent colitis, but it is possible that ipilimumab may be able to be combined safely with dabrafenib.[95] In patients with renal cell carcinoma, the combination of tremelimumab and sunitinib was not found to be tolerable,[96] and the combination of nivolumab with sunitinib and pazopanib, although generally manageable and associated with significant antitumor activity, was also associated with hepatic and renal toxicity that seemed to be higher than with each single agent alone.[97]

Radiotherapy has been shown to result in a number of potentially beneficial immunologic effects, as reviewed by Formenti and Demaria.[98] Preclinical studies also suggest the possibility that radiotherapy can enhance the efficacy of CTLA-4 and PD-1 blockade.[99,100] Although some clinical cases and retrospective series suggest that radiotherapy may have enhanced the efficacy of immune checkpoint blockade in patients and is generally believed to be safe,[101-105] prospective trials are under way to test this hypothesis, and no data are yet available.

CTLA-4 blockade has also been administered together with other immunologic agents, such as the indoleamine 2,3-dioxygenase inhibitor INCB024360,[106] the oncolytic virus talimogene laherparepvec,[107] and granulocyte-macrophage colony-stimulating factor,[108] with encouraging early results. We expect subsequent studies involving engineered T-cell–based therapies and checkpoint blockade.

Other promising data involve CTLA-4 combinations with PD-1 blockade. A phase I study of ipilimumab and nivolumab in patients with melanoma resulted in a high durable response rate and impressive overall survival compared with historical data.[109,110] Although the most recently reported grade 3 or 4 toxicity rate in patients with melanoma was 64%, which is higher than either ipilimumab or nivolumab individually,[111] the vast majority of these irAEs were asymptomatic laboratory abnormalities of unclear clinical consequence. For example, elevations in amylase or lipase were reported in 21% of patients, none of whom met clinical criteria for a diagnosis of pancreatitis. The rate of grade 3 or 4 diarrhea was 7%, which is approximately similar to the rate of grade 3 or 4 diarrhea with ipilimumab monotherapy at 3 mg/kg. Whether ipilimumab and nivolumab improve overall survival compared with either nivolumab or ipilimumab alone remains the subject of an ongoing phase III randomized trial, and investigations of the combination of ipilimumab and nivolumab (and tremelimumab and MEDI4736) are ongoing in many other cancers.

CONCLUSION

Immunotherapy with checkpoint-blocking antibodies targeting CTLA-4 and PD-1/PD-L1 has improved the outlook for patients with a variety of malignancies. Despite the promise of this approach, many questions remain, such as the optimal management of irAEs and how best to evaluate combination approaches to determine whether they will increase the efficacy of CTLA-4 or PD-1/PD-L1 blockade alone. Themes from the experience with CTLA-4 and PD-1/PD-L1 will likely be relevant for investigations of novel immunologic checkpoints in the future.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
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