

## EDITORIALS



## Tumor Immunotherapy Directed at PD-1

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The treatment of cancer by harnessing immune responses has long been pursued. Efforts to turn on the immune system against cancers with inactivated tumor vaccines or intratumor injections of bacterial products to induce local inflammation and recruit an antitumor immune response have led to anecdotal successes. Increasing knowledge about how the immune system is activated, coupled with advances in recombinant DNA technology, has allowed the clinical testing of immune-stimulating cytokines such as interferons and interleukins. These trials have led to a low frequency of durable tumor responses in selected cancers such as melanoma and renal-cell carcinoma at the expense of serious toxic effects. The finding that dendritic cells play a central role in orchestrating a T-cell response to cancer has resulted in multiple clinical trials of dendritic-cell-based vaccines. These studies again provided evidence of occasional tumor responses in a minority of patients.<sup>1</sup>

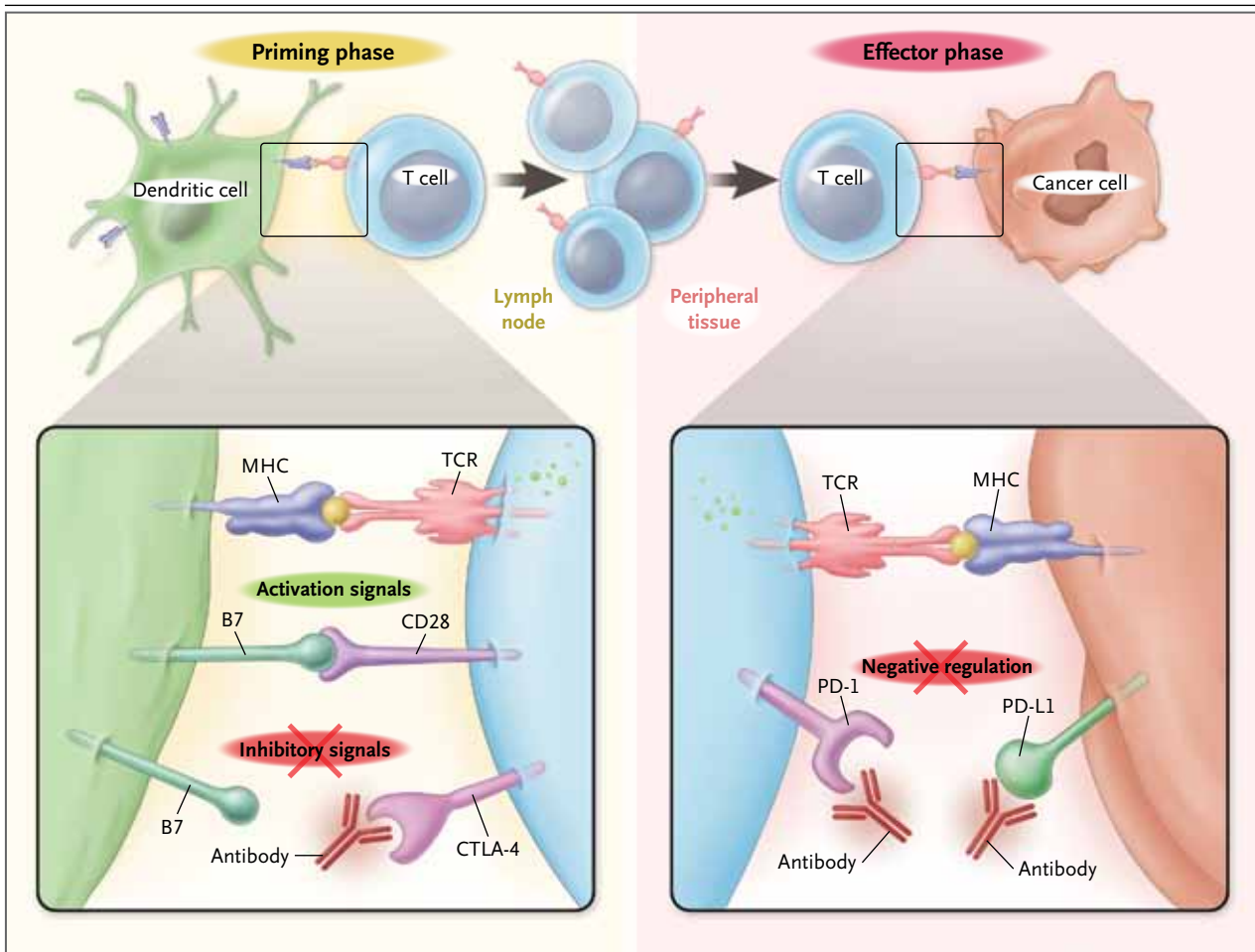
A major limitation of the various approaches to turning on an immune response to cancer is that the immune system exerts a major effort to avoid immune overactivation, which could harm healthy tissues. Cancer takes advantage of this ability to hide from the immune system by exploiting a series of immune escape mechanisms that were developed to avoid autoimmunity. Among these mechanisms are the hijacking of immune-cell-intrinsic checkpoints that are induced on T-cell activation.<sup>2</sup>

Blockade of one of these checkpoints, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), provided the first evidence of improvement in overall survival for the treatment of patients with metastatic melanoma.<sup>3,4</sup> The coinhibitory receptor CTLA-4 predominantly regulates T cells at the

stage of initial activation by competing with the CD28+ costimulatory receptor for binding of CD80 (B7-1) and CD86 (B7-2) expressed by antigen-presenting cells such as dendritic cells (Fig. 1). CTLA-4 is expressed approximately 48 hours after T-cell activation and provides dominant negative signaling. Inhibition of CTLA-4 by blocking antibodies such as ipilimumab or tremelimumab results in objective response rates of 10 to 15% in patients with metastatic melanoma, a response that is associated with clinically significant inflammatory or autoimmune toxic effects in 20 to 30% of patients.<sup>2</sup>

The programmed death 1 (PD-1) receptor is another inhibitory T-cell receptor that is engaged by its two known ligands, PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273), primarily within the tumor microenvironment (Fig. 1).<sup>2,5</sup> The increased selectivity for immune suppressive signals that are delivered directly by the cancer, together with the role of PD-1 in regulating predominantly the effector phase of T-cell responses, predicts that PD-1 inhibition will have fewer side effects and greater antitumor activity than CTLA-4 inhibition.<sup>2,6</sup> PD-1 was discovered in 1992 by Honjo and colleagues, who were studying mechanisms of T-cell death.<sup>6</sup> Since then this immune regulatory receptor has been shown to have a critical role in autoimmunity, infectious immunity, transplantation immunity, and allergy, in addition to the demonstration of its blockade in tumor immunotherapy.<sup>7-9</sup> PD-1 activities include the inhibition of T cells during long-term antigen exposure, as happens in chronic viral infections<sup>10</sup> and cancer.<sup>2</sup>

As now reported in the *Journal*, large clinical trials of anti-PD-1 antibody by Topalian et al.<sup>8</sup> and anti-PD-L1 antibody by Brahmer et al.<sup>9</sup> show that



**Figure 1. Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.**

T cells recognize antigens presented by the major histocompatibility complex (MHC) on the surface of cancer cells through their T-cell receptor (TCR). This first signal is not enough to turn on a T-cell response, and a second signal delivered by the B7 costimulatory molecules B7-1 (or CD80) and B7-2 (or CD86) is required. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is up-regulated shortly after T-cell activation and initiates negative regulation signaling on T cells during ligation with the B7 costimulatory molecules expressed by antigen-presenting cells. When these molecules bind to CD28, they provide activation signals; when they bind to CTLA-4, they provide inhibitory signals. The interaction between CTLA-4 and the costimulatory molecules happens primarily in the priming phase of a T-cell response within lymph nodes. Programmed death 1 (PD-1) inhibitory receptor is expressed by T cells during long-term antigen exposure and results in negative regulation on T cells during ligation with PD-L1 and PD-L2, which are primarily expressed within inflamed tissues and the tumor microenvironment. The PD-1 interaction happens in the effector phase of a T-cell response in peripheral tissues. Its blockade with antibodies to PD-1 or PD-L1 results in the preferential activation of T cells with specificity for the cancer.

widely applicable immunotherapy agents have broken the ceiling of durable tumor response rates of 10 to 15% (the highest rate of antitumor activity of the many immunotherapy approaches tested in the clinic for the treatment of cancer during the past 30 years<sup>4</sup>). Furthermore, objective and durable tumor responses were reported in patients with lung cancer, which has been notoriously resistant to immunotherapy.

These initial observations suggest that antibodies blocking PD-1 or PD-L1 are likely to provide a new benchmark for antitumor activity in immunotherapy. An interesting finding was that patients with colon and pancreatic cancers did not have tumor responses after receiving anti-PD-1 or anti-PD-L1 antibodies. It is likely that the antitumor immune activation induced by these antibodies is not a random event but in-

stead may be guided by molecular mechanisms related to the histologic features or oncogenic signaling pathways of the tumor or factors induced within the tumor microenvironment. Understanding the tumor selectivity of PD-1 or PD-L1 antagonistic antibodies provides a great opportunity for selection of patients on the basis of tumor markers. Key to this understanding is the study of the expression of the PD-1 ligands PD-L1 and PD-L2 in the tumor microenvironment. Preliminary evidence suggests that the expression of PD-L1 may indeed select for patients with an improved response to PD-1 axis inhibitors.

The next frontier in the treatment of cancer requires meeting the goal of inducing a high frequency of long-lasting tumor response on the basis of selectable markers in order to personalize therapies. Inhibition of PD-1 may meet these expectations in selected cancers. The immune system remembers what it targets, so once the system is correctly activated, it may mediate a durable tumor response, as demonstrated previously in clinical trials of high-dose interleukin-2 and anti-CTLA-4 antibodies. The durability of the tumor response to anti-PD-1 and anti-PD-L1 antibodies in a great majority of patients who had objective tumor regressions in the studies by Topalian et al. and Brahmer et al. predicts that these antibodies unleash a memory immune response to cancer. The use of PD-1 blockade — with its reduced rate of toxic effects and potential ability to further select patients who have an increased

likelihood of tumor response — may well have a major effect on cancer treatment.

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## Native-Valve Infective Endocarditis — When Does It Require Surgery?

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Guidelines, not backed by evidence from randomized trials, strongly recommend urgent surgery for patients with infective endocarditis and congestive heart failure due to valvular regurgitation.<sup>1,2</sup> Management algorithms for infective endocarditis have been developed, and a recent study showed that surgery is still required in 50% of patients who receive antibiotics.<sup>3</sup> Experience shows that surgery in patients with active infective endocarditis is associated with low mortality.<sup>4</sup>

Debate continues, however, about the timing of surgery to prevent embolic events when there are large or mobile vegetations or vegetations in particular locations and when patients have severe valve dysfunction but do not have heart failure. Postponing surgery on the presumption that operating on a patient with active infection is too risky and technically demanding exposes the patient to the risk of further destruction of cardiac tissue as well as to the potential development of heart failure, atrioventricular block,