

The Future of Cancer Treatment: Will It Include Immunotherapy?

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Negative immune regulatory pathways inhibit anti-cancer T cell responses, preventing effective immune surveillance. Two clinical trials using monoclonal antibodies that antagonize the PD-1/PD-L1 pathway recently reported regression in several tumor types. In one of these trials, efficacy was linked to the expression of the PD-L1 biomarker on tumor cells.

Over the past few decades, we have often heard in the halls of cancer meetings, “Immunotherapy is the future of cancer treatment... and always will be.” The idea that the immune system can be harnessed to destroy tumors has been a dream for over a century, ever since William Coley first injected toxins into patients to treat cancer. Reporting in a recent issue of *New England Journal of Medicine*, [Topalian et al. \(2012\)](#) and [Brahmer et al. \(2012\)](#) explore the clinical effects of two complementary means of achieving anti-tumor immunity in multiple cancers including, for the first time, lung cancer. These trials utilized monoclonal antibodies (mAbs) targeting a cell surface molecule programmed death-1 (PD-1) on T cells and its ligand PD-L1, which is over-expressed on cancer cells. The combination of these results and experiences with ipilimumab, an FDA-approved mAb that targets a related negative regulatory receptor cytotoxic T lymphocyte antigen 4 (CTLA-4), leaves no doubt that the future is here, and with it, a new era in the treatment of cancer.

The modern era of cancer immunology has focused on using immunotherapy to “boost” the immune system through vaccination and adoptive cellular immunotherapy based on the proposition that tumors express antigenic protein targets, but the anti-tumor T cells are not being activated due to limited T cell activation, growth factors, or immunosuppressive molecules secreted by cancer cells themselves. In many instances, these efforts have focused on promoting key positive co-stimulatory and innate immune pathways (such as ICOS, CD28, CD154, and

TLR ligands) that are critical for a potent and sustained immune response. The general thinking was that the immune system was the lack of recognition and induction of an anti-tumor response. However, in the mid-90’s, it became clear that the immune system did indeed recognize tumor antigens (mostly overexpressed self proteins) but remained quiescent in spite of the persistent presence of tumor antigens. This led to the hypothesis that there must be an active brake on the anti-tumor response that shuts down active immunity. The breakthrough came when it was discovered that negative regulatory T cell surface molecules (the first of which was CTLA-4) were upregulated in activated T cells to dampen their activity, resulting in less effective killing of tumor cells ([Walunas et al., 1994](#), [Leach et al., 1996](#)). These inhibitory molecules, termed negative co-stimulatory molecules due to their homology with the quintessential T cell co-stimulatory molecule CD28, included a number of related family members including PD-1, B7-H4, B- and T-lymphocyte attenuator (BTLA), and their ligands ([Bour-Jordan et al., 2011](#)). The molecules function by multiple pathways, including the attenuation of early activation signals, competition for positive co-stimulation, and direct inhibition of the antigen presenting cells that would otherwise promote immune responses. The importance of these pathways was highlighted by studies showing that total blockade via genetic disruption led to massive T cell hyperproliferation and protracted multiorgan autoimmunity. Thus, it became increasingly clear that there

were a series of major pathways that the immune system employs to avoid unwanted autoimmune or hyperimmune responses. In various animal models, administration of immune checkpoint inhibitors (ICI) unleashed immunity to tumors, viruses, and other pathogens. These seminal studies ultimately led to the development and FDA approval of the first antibody-based immunotherapy that targets negative co-stimulation ipilimumab (Yervoy) in patients with metastatic melanoma ([Hodi et al., 2010](#)).

The first clinical trials of ICI-specific mAbs against the receptor PD-1 and its ligand PD-L1 included subjects with late-stage, heavily-pretreated kidney, lung, prostate, and colon cancer. They took advantage of newly conceived adaptive trial designs to move rapidly from a dose finding mode in multiple tumor types to rapid efficacy expansion cohorts ([Wolchok et al., 2009](#)). The data are quite encouraging and go beyond typical expectations. Overall, approximately 20%–25% of patients with metastatic melanoma, kidney (renal cell) and lung (non-small cell) cancer had partial or complete tumor shrinkage. Importantly, the durability of the responses was unparalleled as 65% of patients followed for greater than one year remained responsive ([Topalian et al., 2012](#); [Brahmer et al., 2012](#)). The relatively low responses of the lung cancer patients to the PD-1 pathway immunotherapy is an important starting point for developing treatments that couple the ICIs with other therapies.

While these trials were highlighted for their success, it must be noted that the inherent risk in approaches that harness

the immune system to target anti-tumor immunity is the development of autoimmunity. While ipilimumab and these antibodies have not been directly compared, there appears to be less severe immune-related toxicity with the anti-PD-1 and anti-PD-L1 mAbs. Nevertheless, grade 3 and 4 toxicity did occur in 9% (Brahmer et al., 2012) and 11% (Topalian et al., 2012) of patients, and episodes of presumed autoimmune pneumonitis, including some with fatal outcomes, colitis, hepatitis, hypophysitis, and thyroiditis were noted. Importantly, autoimmunity can usually be treated with immune suppressive therapy without an apparent effect on anti-cancer immunity. The finding that the autoimmune side-effect profile is different between the different ICI drugs raises the question as to whether this is due to more “downstream” and specific roles of the PD-1-PD-L1 interaction in cancer.

It is important to note that the effect of these drugs represents a growing class effect, as demonstrated by the clinical activity of ipilimumab in renal cell carcinoma, prostate cancer, and melanoma. In addition, inhibitors of other targets, such as TIM-3, BTLA, etc., are working their way through pre-clinical and clinical development (Norde et al., 2012). As is the case with ipilimumab, treatment with anti-PD-1 and anti-PD-L1 mAbs did not appear to benefit patients with prostate or colon cancer. However, the responses in melanoma and kidney cancer were greater than that seen with ipilimumab.

The reason for these differences remain unclear, but it is important to note that there appeared to be a correlation between patient response and the expression level of PD-L1 on the tumor cells in the anti-PD-1 study (Topalian et al., 2012). In preliminary results, 9 of 25 (36%) patients with PD-L1 positive cancers had an objective response, whereas none of the 17 patients whose tumors were PD-L1 negative had an objective response. The results suggest that receptor-target localization may define key differences in the efficacy of these agents, as CTLA-4 ligands and PD-1 ligands are differentially expressed on hematopoietic cells versus stromal cells, respectively. Moreover, the PD-1-PD-L1 pathway preferentially controls effector-memory CD8⁺ T cell responses at the tissue site, while CTLA-4, via interaction with CD80 and CD86, has been shown to control early T cell responses in lymphoid tissues (Jin et al., 2011; Egan et al., 2002). Finally, the use of ICIs in combination with specific tumor and tumor antigen immunization may prove extremely effective in these therapeutic settings to boost existing responses and initiate de novo immunity.

In summary, these two studies provide compelling evidence that immunotherapy is no longer the future of cancer treatment, but is very much a current reality. The articles by Brahmer et al. (2012) and Topalian et al. (2012) provide critical insights into how further understanding of the basis of cancer immu-

nology will lead to advances that benefit our patients.

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