PD-1: Another Immune Inhibition for T Cell Therapeutics for Melanoma

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There has been a great deal of development of therapeutics for melanoma utilizing the immune system against the metastatic cells. We discuss here two new therapeutics both of which target PD-1 receptors, inhibiting them and thus allowing the activation of the T cell against the melanoma.

PD-1: ANOTHER IMMUNE INHIBITION FOR T CELL THERAPEUTICS FOR MELANOMA

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1 INTRODUCTION

There seems to be an increasing competition between pathway inhibitors and immune system enhancers in the treatment of melanoma. Two papers, one by Wolchok et al and the other by Hamid et al have shown significant progress in the immune portion.

CTLA-4 and PD-1 can be inhibited and such inhibition allows T cells to function by attacking the malignant cells. In effect we have re-activated the immune system to go after the cancer cells. Thus there is considerable interest in enabling the T cells in the immune system to identify the malignant cells and target them for elimination. This has long been a desired goal, with Rosenberg at NCI, being one of the major promoters. The key issue here, however, is that this approach assumes all cancer cells are alike, namely intruders, and that the immune system if properly activated can attack.

As NEJM states:

Wolchok et al. and Hamid et al. report in the Journal the results of phase 1 clinical trials showing that the combination of PD-1 and CTLA-4 antibody blockers leads to improved treatment outcomes in patients with melanoma, without an escalation of toxic effects.

The results of these trials are striking and complementary. In the trial by Hamid et al., a PD-1 monoclonal antibody was administered in patients who had had a relapse after CTLA-4 antibody monotherapy (ipilimumab); the authors found that durable and clinically significant responses were as common and robust as were those observed in patients who had not received ipilimumab therapy previously. Thus, progression of melanoma after anti-CTLA-4 therapy does not preclude a response to anti-PD-1 therapy.

Wolchok et al., who in part report similar data for sequential CTLA-4 and PD-1 antibody therapy, also tested concomitant administration and found that at the maximum tolerated dose, 53% of patients with advanced, treatment-resistant melanoma had objective tumor responses, with tumor regression of at least 80% in every patient who had a response.

Surprisingly and importantly, the use of ipilimumab and either one of two PD-1 monoclonal antibodies — whether the PD-1 and CTLA-4 antibodies were given sequentially or together — resulted in a rate and severity of adverse events that were no higher than those observed with the individual drugs alone.

It is expected that from these trials we can eventually see a combination therapy and then a selected genetic individual therapy.

Finally as NEJM so properly puts it:

The clinical successes of CTLA-4 and PD-1 antibody immunotherapy in cancer are the outcomes of the correct recognition of the therapeutic potential of the molecules at the time of discovery, preclinical studies that showed high therapeutic potential, and well-designed and well-executed

clinical trials. This partnership of basic science, translational science, and clinical medicine should be celebrated.

These two papers focus on the immune system approach. We have seen that if we can combine this approach with the pathway blocking approach that perhaps there may be some added efficacy, yet the results are not yet in.

Now PD-1 has been a target for therapeutics for a while. As Ascierto et al state:

Treatment for both early and advanced melanoma has changed little since the introduction of interferon and IL-2 in the early 1990s. Recent data from trials testing targeted agents or immune modulators suggest the promise of new strategies to treat patients with advanced melanoma.

These include a new generation of B-RAF inhibitors with greater selectivity for the mutant protein, c-Kit inhibitors, anti-angiogenesis agents, the immune modulators anti-CTLA4, anti-PD-1, and anti-CD40, and adoptive cellular therapies. The high success rate of mutant B-RAF and c-Kit inhibitors relies on the selection of patients with corresponding mutations. However, although response rates with small molecule inhibitors are high, most are not durable. Moreover, for a large subset of patients, reliable predictive biomarkers especially for immunologic modulators have not yet been identified.

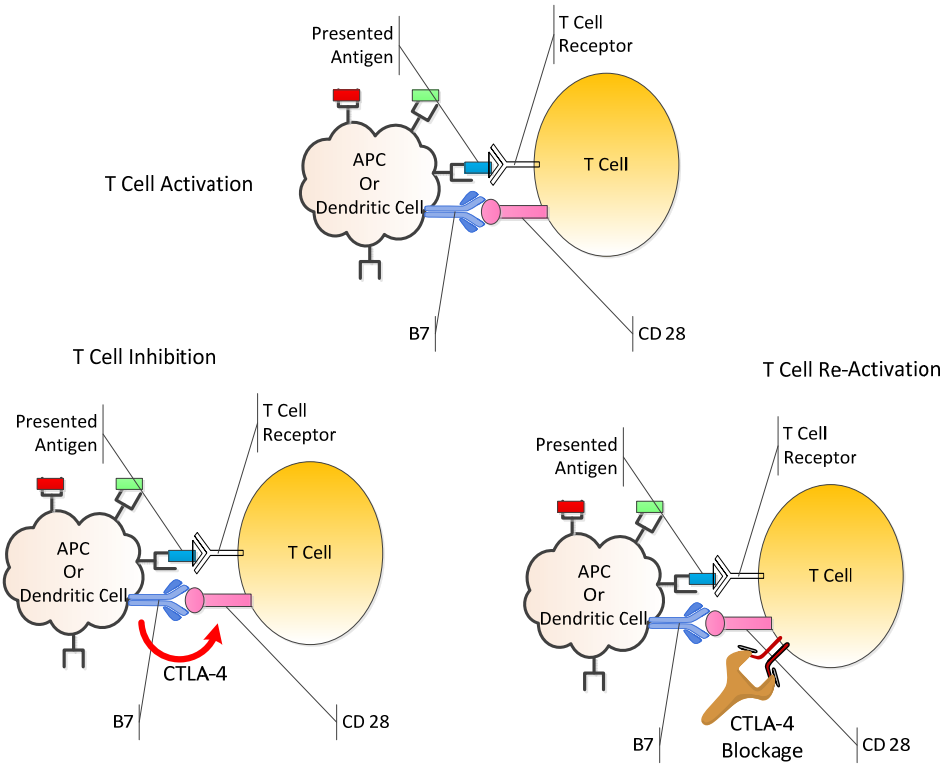
Progress may also depend on identifying additional molecular targets, which in turn depends upon a better understanding of the mechanisms leading to response or resistance. More challenging but equally important will be understanding how to optimize the treatment of individual patients using these active agents sequentially or in combination with each other, with other experimental treatment, or with traditional anticancer modalities such as chemotherapy, radiation, or surgery.

Compared to the standard approach of developing new single agents for licensing in advanced disease, the identification and validation of patient specific and multi-modality treatments will require increased involvement by several stakeholders in designing trials aimed at identifying, even in early stages of drug development, the most effective way to use molecularly guided approaches to treat tumors as they evolve over time.

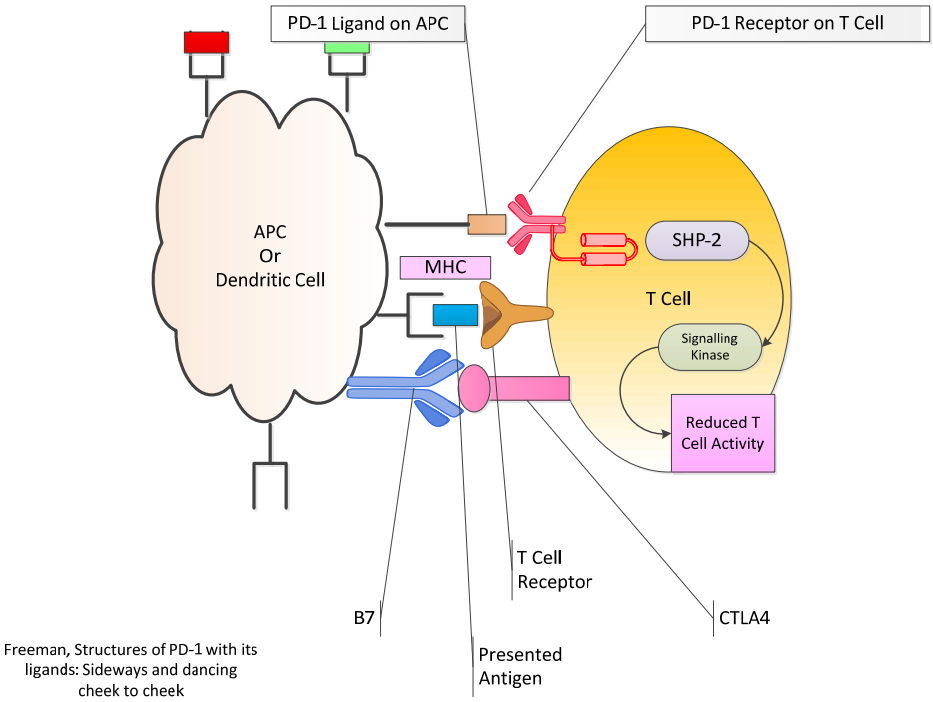
The question remaining is; which approach is better or best, immune activation or pathway inhibition, or both? Or, are there other altogether different options? This is the challenge that we see in this area.

2 PD-1 PATHWAYS

Let us begin with a brief review of PD-1 pathways. We have previously discussed the CTLA-4 blockage and the current approaches used to inactivate that element of T cell suppression. We summarize that again in the figure below.



Now CTLA-4 is not the only inhibitor of T cell action. PD-1 also can be activated and thus suppress T cell activity. This means that is we can find a way to inactivate or inhibit PD-1 then we have another way to seek possible activation of the T cells. In fact perhaps we can do both and secure a super active T cell base. That is in essence the Wolchok approach. We depict this in the figure below.



Freeman, Structures of PD-1 with its ligands: Sideways and dancing cheek to cheek

The paper by Okazaki and Honjo in 2007 also details many of the critical elements regarding the PD-1 and its ligands. It details many of the recognized disease states as well. As they state:

Since the discovery of PD-1 in 1992, the biological function of PD-1 remained mystery for many years. Generation of Pdcd1mice and the discovery of its ligands turned around the situation and the function of PD-1 was unveiled thick and fast in these 5 years. Consequently, it became clear that PD-1 plays critical roles in the regulation of autoimmunity, tumor immunity, infectious immunity, transplantation immunity, allergy and immune privilege. The development of autoimmune diseases by Pdcd1 mice especially enchanted clinicians and promoted clinical research as well.

Currently, many groups are trying to generate not only PD-1 antagonists for the treatment of cancer and infectious diseases but also PD-1 agonists for the treatment of autoimmune diseases, allergy and transplant rejection. Among these, humanized antibody against human PD-1 was approved by Food and Drug Administration of the United States as an investigational new drug in August 1, 2006. Clinical trials will test its clinical efficacy on cancer and infectious diseases.

Now we can examine the features of PD-1. As Freeman states:

T cell activation requires a TCR mediated signal, but the strength, course, and duration are directed by costimulatory molecules and cytokines from the antigen-presenting cell (APC). An unexpected finding was that some molecular pairs attenuate the strength of the TCR signal, a process termed co-inhibition.

The threshold for the initiation of an immune response is set very high, with a requirement for both antigen recognition and costimulatory signals from innate immune recognition of ''danger'' signals. Paradoxically, T cell activation also induces expression of co-inhibitory receptors such as programmed death-1 (PD-1).

Cytokines produced after T cell activation such as INF- and IL-4 up-regulate PD-1 ligands, establishing a feedback loop that attenuates immune responses and limits the extent of immune-mediated tissue damage unless overridden by strong costimulatory signals. PD-1 is a CD28 family member expressed on activated T cells, B cells, and myeloid cells. In proximity to the TCR signaling complex, PD-1 delivers a co-inhibitory signal upon binding to either of its two ligands, PD-L1 or PD-L2.

Engagement of ligand results in tyrosine phosphorylation of the PD-1 cytoplasmic domain and recruitment of phosphatases, particularly SHP2

Additional insight can also be provided by examining the regulatory T cells as well. As Francisco et al state:

Regulatory T cells (Tregs) and the PD-1: PD-ligand (PD-L) pathway is both critical to terminating immune responses. Elimination of either can result in the breakdown of tolerance and the development of autoimmunity. The PD-1: PD-L pathway can thwart self-reactive T cells and protect against autoimmunity in many ways. In this review, we highlight how PD-1 and its ligands defend against potentially pathogenic self-reactive effector T cells by simultaneously harnessing two mechanisms of peripheral tolerance: (i) the promotion of Treg development and function and (ii) the direct inhibition of potentially pathogenic self-reactive T cells that have escaped into the periphery.

Treg cells induced by the PD-1 pathway may also assist in maintaining immune homeostasis, keeping the threshold for T-cell activation high enough to safeguard against autoimmunity. PD-L1 expression on non-hematopoietic cells as well as hematopoietic cells endows PD-L1 with the capacity to promote Treg development and enhance Treg function in lymphoid organs and tissues that are targets of autoimmune attack. At sites where transforming growth factor-β is present (e.g. sites of immune privilege or inflammation), PD-L1 may promote the de novo generation of Tregs.

3 THERAPEUTICS

There have been two recent papers describing two separate therapeutics focusing on PD-1. We examine them both as follows.

3.1 LAMBROLIZUMAB

First we will start with the Hamid et al paper and their use of Lambrolizumab. This is an inhibitor of PD-1. This Trial is a single agent trial and has demonstrated significant efficacy in melanoma treatment.

As Hamid et al state:

The programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer. We tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma.

Cancer evolves to exploit multiple mechanisms in order to avoid immune cell recognition and antitumor effector functions, thereby limiting the clinical benefits of immunotherapy strategies. Antibodies that block the inhibitory receptor cytotoxic T-lymphocyte– associated antigen 4 (CTLA-4), such as ipilimumab, have been shown to release one of these negative immune regulatory pathways, leading to durable responses in a subgroup of patients with metastatic melanoma and an overall survival benefit in patients with metastatic melanoma.

The programmed cell death 1 (PD-1) receptor is another inhibitory receptor expressed by T cells preferentially with long-term exposure to antigens. Its primary ligand, PD-L1 (also known as B7-H1 or CD274), is frequently expressed within the tumor microenvironment, including cancer cells and tumor-infiltrating macrophages.

The PD-1 receptor has a second ligand, PD-L2 (also known as B7-DC or CD273), that is preferentially expressed by antigen-presenting cells.3 In tumor models, PD-1 negatively regulates the effector phase of T-cell responses after ligation of PD-L1 expressed within the tumor.4 It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systemic toxic effects than those that are seen with other immune checkpoint inhibitors.

Lambrolizumab (previously known as MK-3475) is a highly selective, humanized monoclonal IgG4–kappa isotype antibody against PD-1 that is designed to block the negative immune regulatory signaling of the PD-1 receptor expressed by T cells.

3.2 NIVOLUMAB

The second paper is a dual agent trial headed by Wolchok at Sloan Kettering. This trial used a PD-1 inhibitor Novolumab along with the now used Ipilimumab. As Wolchok et al state in their paper:

In patients with melanoma, ipilimumab (an antibody against cytotoxic T-lymphocyte– associated antigen 4 [CTLA-4]) prolongs overall survival, and nivolumab (an antibody against the programmed death 1 [PD-1] receptor) produced durable tumor regression in a phase 1 trial. On the basis of their distinct immunologic mechanisms of action and supportive preclinical data, we conducted a phase 1 trial of nivolumab combined with ipilimumab in patients with advanced melanoma.

We had previously examined Ipilimumab and its functions and have further demonstrated how it can be used with PD-1 inhibitors. The combination of these two should increase the overall T cell response. They continue:

Nivolumab, a fully human IgG4 antibody blocking the programmed death 1 (PD-1) receptor, produced durable objective responses in patients with melanoma, renal-cell cancer, and non–small-cell lung cancer. CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation.

In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone. On the basis of these observations, we conducted a phase 1 study to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in patients with advanced melanoma. Data for 86 patients treated in this ongoing study are reported.

The interesting fact to note is that the combination does increase T cell response. The question is why? Are the T cells different, and if so why, and what makes them different. Are we dealing with a secondary effect or is this primary?

The observation that patients can have objective responses when treated with nivolumab after previous treatment with ipilimumab indicates that a lack of response to CTLA-4 blockade does not preclude a clinical benefit of PD-1 blockade and further supports the nonredundant nature of these coinhibitory pathways. Data from previous studies suggest a potential association between the occurrence of a response and tumorcell expression of PD-L1 in patients receiving nivolumab and a correlation between overall survival and increases in the peripheral-blood absolute lymphocyte count in patients treated with ipilimumab.

4 OBSERVATIONS

The NY Times has an article on Cancer Therapeutics, following the annual ASCO Conference in Chicago[1]. Regrettably the focus is on immune system therapeutics almost exclusively. In fact there is a quote:

The new drugs work by disabling a brake on the immune system called the programmed death 1 receptor, or PD-1. And although the data presented at the meeting was from the earliest stage of testing only, the drugs were the center of attention here, with some doctors predicting that cancer treatment was about to shift.

"If you look five years out, most of this meeting will be about immunotherapy," said Dr. Mario Sznol, a professor of medical oncology at Yale.

This is akin to Rosenberg some twenty five years ago, a dream that the immune system alone will be the means to the end. Somehow this article fails to account for the pathway blockers such as those blocking BRAF and MEK.

The article continues:

Harnessing the immune system is appealing for several reasons. It might be applicable to many different types of cancer. It might produce longer lasting remissions than can be achieved by chemotherapy or the newer targeted drugs. And it seems somehow more natural and holistic.

This is a classic statement of those seeking the Holy Grail. In reality one suspects that we will be identifying and targeting mutation after mutation and not just allowing the immune system to respond. After all the PD-1 inhibitor just enables another path to work on T cell attack. This is the second of many possible but T cells are most likely not the sine qua non.

We are still intrigued by TVEC and the viral attack. Perhaps what we will see is a typical combine approach. However there are many approaches and the Press all too often send out hope to patients well ahead of reality. The PD-1 Trials were Phase 1 Trials after all!

[1] http://www.nytimes.com/2013/06/04/health/promising-new-cancer-drugs-empower-the-bodys-own-defense-system.html?hp

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