PD-L1 Inhibitors Update

**Background**

The discovery that many cancer cells array themselves in proteins that stave off an immune system attack stands as one of the most significant advances in the history of cancer research. It has led to a new class of drugs that have scored extraordinary success against a variety of cancer types, including malignant melanoma, for which there previously had been no effective treatment.

The major breakthroughs in this area occurred in the early 2000s, when scientists reported that molecules on the surface of some cancer cells turned off the attack on the cells by immune system T cells. The discovery that they act as a brake on such an attack has forever changed the field of cancer immunotherapy, which enlists the human immune system as a weapon against cancer.

**The discovery of PD-L1**

In 2000, Dana-Farber Cancer Institute’s Gordon Freeman, PhD, and his colleagues published a study announcing the discovery of the protein PD-L1 (programmed cell death 1 ligand 1) on normal cells. The researchers found that PD-L1 exerts an inhibitory effect on T cells by binding to the T cell co-receptor PD-1, thereby signaling the T cell not to instigate an immune system attack.

A year later, Freeman and his colleagues published a follow-up study, reporting that PD-L1 appears not only on some normal cells but on certain cancer cells as well. They called this “cancer’s shield against the immune system.” The implication was that an agent that blocks PD-L1 (or a related ligand, PD-L2) could release the brakes on an immune system attack on the cancer.

The discovery led to the development of drugs that block PD-1, PD-L1, or PD-L2, now called checkpoint inhibitors, and a rapid acceleration of clinical research. To date, the U.S. Food and Drug Administration (FDA) has approved six such inhibitors as standard treatment for 21 different types of cancer.

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Clinical testing today

Freeman’s discovery put Dana-Farber investigators at the leading edge of research into checkpoint inhibitors. Today, investigators across the United States are conducting more than 2,500 trials of PD-L1, PD-L2, and PD-1 inhibitors in virtually every type of cancer, including many rare malignancies. Nearly 2,000 of these trials involve combinations of checkpoint inhibitors with other therapies, such as chemotherapy, targeted drugs, radiation therapy, and other types of immunotherapy. Altogether, nearly 400,000 patients are participating in PD-1/L1/L2 trials.

Most of the initial round of clinical trials involved checkpoint inhibitors as single-agent treatments for specific cancer types. In some cancers, particularly Hodgkin lymphoma, the drugs produced striking results. In one trial led by Dana-Farber investigators, the PD-1 inhibitor nivolumab produced full or partial remission in 87 percent of Hodgkin lymphoma patients who had not responded to chemotherapy or a stem cell transplant. By 2017, the drug had been FDA-approved for use in patients with Hodgkin lymphoma, melanoma, non-small cell lung cancer, bladder cancer, kidney cancer, and squamous cell cancer of the head and neck.

For most types of cancer other than Hodgkin lymphoma, response rates to checkpoint inhibitors as single agents are in the 20-25% range. When patients did respond to the drugs, whether with partial or full remissions, the benefits tended to be durable, lasting many months or years. Most often, however, only a moderate percentage of patients benefited from checkpoint inhibitors alone.

Hoping to improve on these results, researchers are now pairing checkpoint inhibitors with other therapies that have the potential to raise the inhibitors’ effectiveness. Some of these therapies can make tumor cells more “visible” — and therefore more vulnerable — to checkpoint inhibitors. Others can bolster the immune system’s attack on cancer cells – an attack made even more potent by the action of checkpoint inhibitors. Combinations of checkpoint inhibitors and other therapies now comprise the majority of clinical trials involving inhibitors.

Examples of such combination trials include:

• A phase I/II study of the PD-L1 inhibitor durvalumab in combination with the targeted drug mocetinostat in patients with...
advanced or metastatic solid tumors and non-small cell lung cancer.  
• A phase II study of the checkpoint inhibitor atezolizumab and chemotherapy in certain patients with advanced urothelial cancer.  
• A phase I/II study of a PD-1/PD-L1 inhibitor in combination with the targeted drug isunakinra in patients with solid tumors.  
• A phase II study of atezolizumab with or without low-dose radiation therapy in patients with relapsed or resistant advanced stage follicular lymphoma.  
• A phase I/II trial of a combination of the PD-1 inhibitor pembrolizumab and the PARP inhibitor niraparib in patients with triple-negative breast cancer or ovarian cancer.

These trials and others will help researchers determine which drugs or combinations are safest and most effective for specific groups of patients, while shedding light on the mechanism by which the drugs work.

In basic research, scientists are working to understand why some patients benefit from checkpoint inhibitors while others don’t, and to translate their findings into more effective therapies. Dana-Farber researcher Jean Zhao, PhD, and her associates, for example, are studying how CDK4/6 inhibitors work together with checkpoint inhibitors in breast cancer. David Barbie, MD, also of Dana-Farber, is studying whether variations in the immune system from one person to another affect individuals’ cancer-fighting ability. Freeman and others are exploring whether newly described checkpoint proteins play a role in turning off an immune system attack and could be targeted in future studies.

Selected References


