

Study finds potential predictive biomarker for response to PD-L1 checkpoint blocker

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F. Stephen Hodi, MD. Credit: Sam Ogden, Dana-Farber

A promising experimental immunotherapy drug works best in patients whose immune defenses initially rally to attack the cancer but then are



stymied by a molecular brake that shuts down the response, according to a new study led by researchers at Dana-Farber Cancer Institute and the Yale University School of Medicine.

The antibody drug, known as MPDL3280A, inhibits the brake protein, PD-L1, reviving the response by immune killer T cells, which target and destroy the <u>cancer cells</u>. In recent clinical trials, the PD-L1 checkpoint blocker caused impressive shrinkage of kidney, melanoma, and lung tumors. But, as with other immunotherapy drugs, many <u>patients</u> saw no benefit.

Researchers report in the November 27 edition of *Nature* that the antibody was most effective when the patients' immune cells surrounding tumors expressed PD-L1 - a sign that a pre-existing <u>immune</u> response had been shut down by PD-L1. There was less tumor shrinkage in patients who never developed an immune response to the <u>cancer</u> - and, as a result, had less PD-L1 in the cancer and surrounding tissues.

"I think this is a launching point to use these findings as a predictive biomarker," said F. Stephen Hodi, MD, of Dana-Farber, senior author of the report. Hodi directs the Center for Immuno-Oncology and the Melanoma Treatment Center at Dana-Farber. First author is Roy Herbst, MD, PhD, chief of Medical Oncology at the Yale Comprehensive Cancer Center.

The scientists studied tumor tissue samples from 175 patients treated in clinical trials with MPDL3280A for advanced non-small cell lung cancer, melanoma, kidney cancer, and other cancers. On average, 18 percent of the patients had complete or partial shrinkage of their tumors, with higher or lower rates in different cancer types. Overall, the treatment was well-tolerated, with few severe side-effects, the report said.



An antibody stain that marked the presence of PD-L1 was applied to tumor samples that had been removed from patients prior to treatment. The stain revealed PD-L1 not only in the cancer cells, but also tumorinfiltrating immune cells (ICs). These are T cells and other cells of the immune response that had invaded the tumor in an attempt to destroy them.

The study found greater responses to the antibody drug in patients whose <u>tumor cells</u> and ICs were high in PD-L1. The scientists also looked at PD-L1 expression in samples taken from tumors while the patients were in treatment. They found that tumors that had shrunk as cells died showed increases in PD-L1 in the cancer and infiltrating immune cells.

From these findings, the researchers concluded that for the MPDL3280A antibody to be effective, the patient must have mounted an immune response that was beaten back by PD-L1. This creates a target for the PD-L1-blocking antibody, which removes the brakes on the response and allows the immune cells to attack the tumor.

The scientists called for further studies to define predictors of the response to PD-L1 blockers. "Understanding the profile of non-responders will likely provide even more valuable information," they said, "possibly revealing the diversity of mechanisms controlling anti-tumor immunity."

- Scientists analyzed tissue samples from patients who had and had not responded to a promising new immunotherapy drug
- They found that patients did best whose cancers had expression of a protein, PD-L1, in <u>immune cells</u> surrounding the tumor cells, to shut down an immune system attack against the cancer
- The study could help identify patients most likely to respond to the new drug, which blocks PD-L1



More information: Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients, *Nature*, 515, 563–567 (27 November 2014) DOI: 10.1038/nature14011

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