

Frontiers in Tumor Immunotherapy: Blockade of the PD-L1 Inhibitory Ligand

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JR Schoenborn

In addition to protecting us from bacterial and viral infections, the immune system is designed to detect and kill cancer cells. Cancer cells frequently display abnormal proteins on their surface, or have altered levels of normal proteins, which alert the immune system into action. However, the immune system's ability to completely eradicate cancer is often impaired by sophisticated strategies that cancer cells use to evade or turn off immune responses. Cancer cells may take advantage of several barriers that prevent autoimmune destruction of healthy normal tissues. Among these checkpoints, the inhibitory receptor PD-1 is upregulated in T-cells that encounter long-term sustained antigen exposure, such as during chronic infections or during cancer development. Engagement of PD-1 by either of its two ligands, PD-L1 or PD-L2, leads to inhibition of T-cell cytokine production and cytotoxicity – two effector functions necessary for T-cells to kill tumor cells. PD-L1 is frequently expressed at high levels by tumor cells or by the tumor microenvironment in response to local inflammatory conditions. Thus,, tumors can use PD-L1 to shut off effector functions of T-cells, preventing sustained antitumor immunity necessary to eradicate the tumor.

To overcome PD-L1-mediated immune suppression and improve the body's natural resistance to cancer, a recent Phase I trial tested a monoclonal antibody to specifically block PD-L1 in 207 patients with advanced cancer. Drs. Scott Tykodi and Laura Chow of the Clinical Research Division, with colleagues at Seattle Cancer Care Alliance and several other national cancer centers, recently reported that patients handled the new cancer immunotherapy well, with generally tolerable and transient side effects. Most adverse events were low grade and were managed by treatment interruption, discontinuation, or in some cases via glucocorticoids or hormone replacement therapy. The adverse events resulting from PD-L1 blockade were generally less frequent and less severe compared to those experienced by patients treated with ipilimumab, a recently approved immunotherapy that blocks the inhibitory co-receptor CTLA-4 that is expressed on T-cells.

Most exciting, however, was the durable tumor regression and prolonged stabilization of patients' disease, particularly in non-small cell lung cancer, where previous immunotherapy attempts have been unfruitful. Blockade of PD-L1 produced complete or partial antitumor responses in 6-17% of all patients with non-small cell lung cancer, melanoma, renal-cell and ovarian cancers. More specifically, an antitumor response was observed in up to 29% of melanoma patients depending on

the dose of the anti-PD-L1 antibody received. An additional 27% of melanoma patients showed stable disease for at least 24 weeks. Among patients with renal-cell cancer, 12% had objective responses lasting 4-17 months, with an additional 41% having stable disease for at least 24 weeks. Despite previous failures in immunotherapy trials, 8-16% of lung cancer patients showed anti-tumor responses following anti-PD-L1 treatment, with 12% of additional patients having stable disease at least 24 weeks.

Together with concurrently published results on an anti-PD-1 phase I clinical trial, these results suggest that antibody-mediated blockade of the inhibitory PD-1/PD-L1 interaction will be a successful new immunotherapeutic approach for several cancer types including melanoma, renal-cell, lung and ovarian cancers. Additional clinical studies will be needed to define which patients will benefit most from anti-PD-L1 blockade, and determine the most effective dose and treatment schedule. Furthermore, because no antitumor responses were observed in patients with colorectal or pancreatic cancer, it will be important to understand the mechanisms that preclude the utility of PD-L1 blockade in these types of cancers.

[Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthi S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. 2012. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *New England Journal of Medicine*. 366:2455-65.](#)

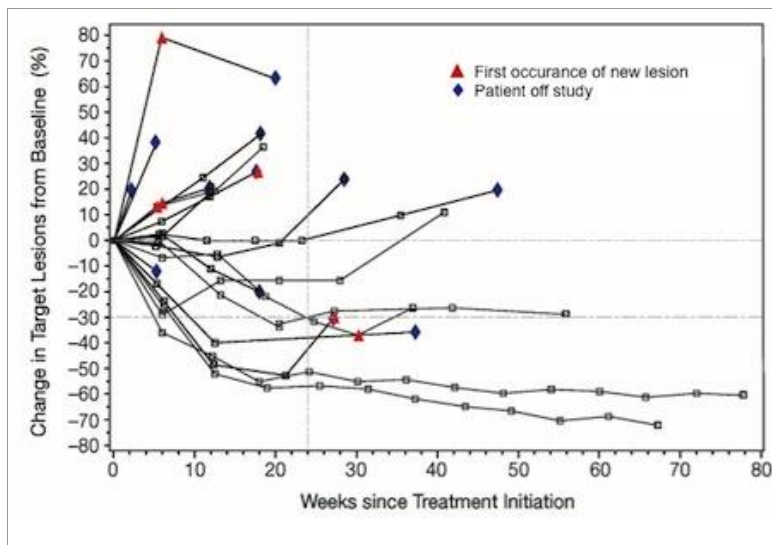


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Evidence for effective immunotherapy in non-small cell lung cancer patients is shown by decreased or sustained tumor burden in patients who received anti-PD-L1 blocking immunotherapy.