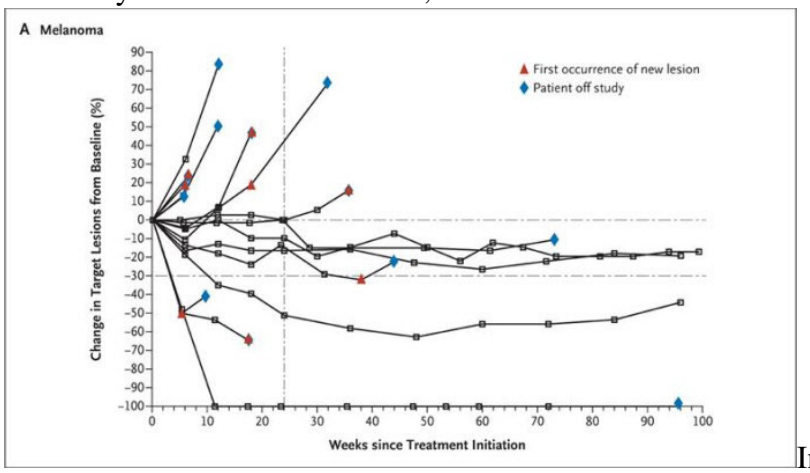
Anti–PD-L1 Antibody in Patients with Advanced Cancer

Posted by Sara Fazio • June 27th, 2012



In the late 19th century, surgical oncologist William Coley reported the story of a patient with a sarcoma whose disease had gone into complete remission following an untreated strep infection at the site of the tumor. At the time, Coley – who had recently witnessed the death of a young patient of his own from the same disease – was searching for new ways to treat the cancer. He wondered if he could replicate the way a strep infection had stimulated the body to fight the sarcoma.

In the decades that followed, Coley went on to inoculate cancer patients with strep cultures, known as "Coley's toxin," with some reports of tumor regression. However, the scientific community was hesitant to adopt the theory that the body's immune response could be co-opted to treat cancer, and Coley's toxin fell out of favor.

Now, more than 100 years later, attempts to stimulate an endogenous immune response have gotten considerably more sophisticated. While monoclonal antibodies against specific tumors, like rituximab, are effective in some settings, investigators have met with less success in their efforts to use T-cell directed immunotherapy. In part this difficulty is related to the immune suppressive effects of the tumor-bearing host. One of the mechanisms by which tumors evade host T cells is by activating "checkpoints" that block T-cell activation. Last year, one such antibody that blocks one of these checkpoints, ipilimumab, which blocks CTLA4 was shown to improve survival in patients with metastatic melanoma. While this antibody has been approved for use in patients, it's not without significant immunological adverse events due to T- cell activation directed against normal self tissues like the colon, liver and thyroid gland.

Thus, the search continues for an agent that can turn on the immune system against the cancer specifically, rather than against itself. Two papers published in this week's issue of NEJM report exciting steps toward that goal.

These two studies both looked at the programmed death 1 (PD-1) receptor as a potential target. This is a second immune checkpoint receptor that is expressed by activated T cells. When the receptor is bound to a ligand, the checkpoint is, essentially, turned on – blocking T-cell activation. Of note, this receptor-ligand pair is more specifically found in tumor cells. Thus, interfering with the binding of receptor to ligand will keep the checkpoint turned off, and, ideally, potentiate antitumor T-cell activation.

These two studies investigated different aspects of this pathway. In one, Julie Brahmer and colleagues gave

patients an intravenous antibody to the PD-1 ligand; in the other, Suzanne Topalian and co-investigators administered an antibody to the PD-1 receptor itself. Both studies demonstrated an objective, "durable" response in a minority of patients treated, all with advanced cancer.

The study led by Brahmer, titled "Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer," enrolled 207 patients; 75 with non-small cell lung cancer, 55 with melanoma and the remainder with colorectal cancer, renal cell, ovarian, pancreatic, gastric or breast cancer. These patients received the study drug every four weeks, and were followed for a median of 12 weeks with a range from two to 111 weeks.

Investigators reported a complete or partial tumor response in a minority of the patients with melanoma, renal-cell, lung and ovarian cancer. These responses lasted for a year in more than half the patients followed for that length of time.

Adverse events most commonly included infusion reactions, diarrhea, rash, nausea, pruritis and headache. While 91% of patients had reported adverse events, the majority were low-grade. By the study's end, 45 patients (22%) had died, most due to progression of disease.

Results in the accompanying Topalian study further validate this mechanism as a promising target for drug development. In that study, 296 patients with cancers including melanoma, lung, prostate, renal-cell and colorectal were given the antibody to PD-1. Nearly a quarter of those with lung cancer, and a slightly larger percentage of those with renal-cell and melanoma, showed a complete or partial response, with most responses lasting a year or longer. Patients with pancreatic or colon cancers did not respond in either study. About one in six patients suffered grade 3 or 4 drug-related adverse events, with three deaths from pulmonary toxicity.

Predicting who will respond to this treatment is not easy. In Topalian's study, none of the patients with PD-L1 negative tumors responded to the drug, but not all patients with positive tumors responded.

These clinical trials have "broken the ceiling of durable tumor response rates," writes Antoni Ribas, a professor of hematology/oncology at UCLA, in an accompanying editorial. He notes that the "new frontier" in cancer will involve treatments that use personalized medicine, based on specific markers, to induce a long-term response. He concludes, "The use of PD-1 blockade – with its reduced rate of toxic effects and potential ability to further select patients who had an increased likelihood of tumor response – may well have a major effect on cancer treatment."

Tags: Anti–PD-L1, Anti–PD-L1 Antibody, cancer, colorectal cancer, ipilimumab, PD-1, PD-1 receptor, rituximab, sarcoma, T-cell directed immunotherapy, William Coley

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