



Mario Sznol, MD

A One-Two Punch Against Melanoma

In a Phase I trial at Yale Cancer Center, a new combination of drugs proved highly effective against an especially dangerous cancer: melanoma. Patients in the trial were treated with two antibodies, ipilimumab and nivolumab. Separately, each drug had shown promise as a cancer-fighter, but together they turned into a powerhouse of immunotherapy.

When cancer cells invade, they send disinformation that tells the body's immune system to turn off. The new drugs work synergistically to block the cancer's disinformation signals and reactivate the body's immune response, which causes T cells to turn back on and start fighting.

"CTLA-4 and PD-1 are two of the most important regulatory checkpoints for immune activation," Mario Sznol, MD, Professor of Medicine, Clinical Research Program Leader of the Melanoma Program, and Co-Director of the Yale SPORE in Skin Cancer explained, "but they work at different places. CTLA-4 – which is blocked by ipilimumab – works earlier in the process, and PD-1 – which is blocked by nivolumab – works a little later to turn off the lymphocytes when they are already around or inside the tumor. Blocking at two different places seems to cause more T cell activity than blocking at only one."

The results of the trial, which began in 2009 and was done jointly with Memorial Sloan-Kettering Cancer Center, were published last summer in

The New England Journal of Medicine. They are impressive. About 70 percent of the patients demonstrated some type of response to the treatment, and many of them benefitted dramatically. In about a third of the patients, the tumors were reduced by 80 percent or more. "And we got the impression that not only were more patients responding," Dr. Sznol said, "but that they were responding faster, and that the amount of tumor reduction was greater than we had seen with either component alone."

The drug combination not only worked fast, it also produced prolonged responses. Most of the responding patients have not had regrowth of their tumors, with follow-up of at least a year and in one patient nearly 3 years. This kind of activity is expected to translate into longer survival. Advanced melanoma is typically fast and deadly, but the one-year survival rate of patients in the trial was about 80 percent.

"That's probably the highest number we've ever seen," Dr. Sznol said. "It's 20 percent higher than the one-year survival that we would have expected with anti-PD-1 alone. In fact, among the first cohort of 25 patients treated at Yale," he added, "about half are now without any evidence of active disease." That sounds very much like a cure, though Dr. Sznol is too cautious a scientist to make that claim – yet. A randomized study is now underway to test the trial's main findings.

The combination of drugs did cause moderate to severe adverse effects in more than half of the

patients. Nivolumab has been very well-tolerated in solo trials, so much of the toxicity seems to be coming from ipilimumab. The question is always whether the benefits outweigh the adverse effects. Dr. Sznol said that he and most of the patients would answer with an emphatic yes. Doctors eventually get the bad side effects under control, and meanwhile the drugs are shrinking most patients' tumors and very likely extending most patients' lives. "I think most of the patients are very happy," Dr. Sznol said, "because they have done very well. It's kind of amazing."

Also amazing, he noted, is how quickly advances have occurred in the treatment of melanoma. Before the FDA approved ipilimumab two years ago, the best drug available for melanoma was the 20-year-old workhorse interleukin-2. Nivolumab could be approved within a year.

The promising combination of ipilimumab and nivolumab is now being tested, or soon will be, on other cancers at Yale – lung cancer, renal cancer, pancreatic cancer, and glioblastoma, among others. "But this isn't the only combination," Dr. Sznol explained, "and it may not even be the best combination. I think we're just scratching the surface of the potential of these approaches." He believes that immunotherapy will soon become the dominant method of treating cancer. "Over time," he said, abandoning caution for just a moment, "one can almost envision an endgame."