Vogelstein nonetheless shot off a letter on the matter to NEJM. The journal promptly rejected their proposal.

Still, Diaz believed he was onto something, and he had found an enthusiastic sounding board for his ideas. Vogelstein—and, independently, Ludwig San Diego Director Richard Kolodner—had in the early 1990s discovered the genetic basis of an inherited propensity for colon cancer known as Lynch syndrome. They had shown that Lynch patients had defects in genes that repair DNA, making them prone to mutations of all sorts, including those that cause cancer.

Diaz, who specializes in treating colon cancer, also knew that the tumors of Lynch patients tended to be highly infiltrated with immune cells and that these patients live longer with their cancers than do most other colon cancer patients. Meanwhile, clinical studies were showing that melanomas respond quite well to PD-1 blockade. These tumors, like those of tobacco-related lung cancers, are known to have highly mutated cells.

**BETTER TOGETHER**  Jedd Wolchok and Stephen Hodi

The evaluation of mechanistically distinct immunotherapies in combination for a variety of cancer types is among the most intriguing trends in cancer research. Jedd Wolchok of Ludwig MSK and Stephen Hodi of Ludwig Harvard are among the pioneers of the strategy, testing the effects of combination checkpoint blockade in patients with advanced melanoma. In 2015, they caused a bit of a stir in the medical community with their publication of the results of a multicenter, Phase 3 trial they led.

The study, which was funded by Bristol-Myers Squibb showed that a combination of the CTLA-4 inhibitor ipilimumab and PD-1 inhibitor nivolumab induces more frequent responses and considerably longer progression-free survival in patients with advanced melanoma than the administration of either of them alone. Published in the *New England Journal of Medicine*, these results prompted the US Food and Drug Administration to approve the combination for patients with advanced, inoperable melanoma.

Wolchok, Hodi and their colleagues found that for ipilimumab alone, the median overall progression-free survival (PFS)—the length of time following treatment before the cancer resumes its growth—was 2.9 months. Patients treated with nivolumab alone had a median PFS of 6.9 months, while the combination of the two resulted in a PFS of 11.5 months. The team also reported that 19% of patients treated with ipilimumab alone and 44% treated with nivolumab had an objective response to each therapy, measured as a significant reduction in tumor size. The response rate for the combination therapy was 58%.

CTLA-4 is a protein found on T cells, which can destroy cancerous and diseased cells. When switched on, it tamps down T cell activity. PD-1, also found on the surface of T cells,
He and Vogelstein began discussing the idea with colleagues at Johns Hopkins. They learned in those discussions that anti-PD1 antibodies had generally failed to induce responses in one trial involving colon cancer patients. But, in a casual hallway conversation, Diaz learned that one patient out of the 33 enrolled in that trial had in fact responded rather well. Diaz asked that the tumor sample from that patient be tested for its mutational load.

“Colon cancer cells typically only have a few dozen mutations,” says Diaz. “But we were thinking, maybe that patient’s tumors had mismatch repair deficiencies and would harbor thousands of mutations per cell. And, lo and behold, that turned out to be the case.”

Excited, Diaz and Vogelstein asked Merck—which makes pembrolizumab—and other companies making anti-PD-1 antibodies whether they would be interested in supporting a trial testing his idea. The answer was, uniformly, no. Coaxed and cajoled by Diaz, however, Merck finally gave in a little: it would donate the drug, but Diaz would

is activated by a protein known as PD-L1, an event that prompts T cells to self-destruct. Both proteins prevent excessive autoimmunity and the destruction of healthy tissues following immune responses to infections. Many tumor cells, however, hijack this protective mechanism and express PD-L1 to thwart T cell attack.

Since its FDA approval, the combination therapy has been welcomed by oncologists, who need every edge they can get against this remarkably aggressive malignancy.

“It has definitely caught on,” says Wolchok. “Here at MSK it’s our go-to option for people who we feel have the medical reserve for some of the side effects that may occur with the treatment.” Those side effects, he points out, can be managed in many patients.

Wolchok, Hodi and their colleagues continue to collect data on the overall survival of patients who participated in the Phase 3 trial.