The therapeutic weapons against various cancers have been multiplying rapidly, but for patients with urothelial bladder cancer (UBC), the options have barely improved in 30 years. Worse, the standard chemotherapy treatment for UBC is too toxic for many patients, whose prognosis is already poor, and although the majority of patients initially respond, most relapse. These limitations may soon change if research on a new immunotherapy lives up to its exciting early promise.

The findings, which emerged from a Phase I trial at Yale Cancer Center and other international cancer centers, caused a stir in June at the annual meeting of the American Society of Clinical Oncology and were published in November in *Nature*. In Yale’s part of the trial, Dr. Daniel Petrylak, MD, Professor of Medicine and Urology, Clinical Research Program Leader for the Prostate and Urologic Cancers Program, and Co-Director of the Signal Transduction Program, and his colleagues tested a new antibody on 15 patients whose metastatic urothelial bladder cancer had not been reduced by chemotherapy, typically the final option for such patients.

“We found a very high response rate,” said Dr. Petrylak. “After twelve weeks of treatment, more than half of the patients had at least a 50 percent decline in their tumor measurements. Two patients had complete disappearance of the tumor. One patient had a cancerous lymph node in his neck, which had completely disappeared, this patient had been on three previous chemotherapies. This was the first time we’ve seen this dramatic a response in patients at this stage of the disease.”

The patients were treated with a new synthetic ‘checkpoint blocking’ antibody called MPDL3280. It targets a protein named PD-L1 (programmed death-ligand 1) that is expressed by some patients’ bladder cancers. About half of the people in Yale’s study were positive for PD-L1 expression, and they responded most strongly to MPDL3280. PD-L1 binds to the surface of bladder cancer cells and sends out disinformation that lulls the immune system into shutting down, which allows the cancer cells to proliferate without interference. MPDL3280 prevents PD-L1 from binding to its receptors and thus short-circuits its deceitful signals. The immune system wakes up, detects the cancer cells, and sends T-cells to destroy them.

The responses among the patients at Yale were not only dramatic, but also prolonged. The trial was designed to treat the patients every three weeks for up to a year, but that has been extended, explained Dr. Petrylak, “because the patients’ tumors are still responding, and because we really don’t know the optimal duration at this point.”

One of his patients, Peter Ehmer, now 44, was diagnosed in May 2013 with stage III bladder cancer. He had three months of chemotherapy and surgery to remove his bladder and prostate. He then participated in a different clinical trial at Yale. Nevertheless, two lymph nodes continued to grow. After three treatments with MPDL3280, he had a CT scan.

“Dr. Petrylak called within an hour,” said Mr. Ehmer, “to say that the lymph nodes had not just shrunk but disappeared. I was very emotional. I called my wife right away and shared the news with my two kids when I got home. I’ve been through a lot in the last year and a half, and it’s just such a weight off my shoulders.”

Mr. Ehmer also confirms another pleasing finding: the side effects of the new immunotherapy, mainly fatigue, are far less severe than those common in chemotherapy. These strong Phase I findings led the U. S. Food and
Drug Administration (FDA) to designate MPDL3280A a ‘Breakthrough Therapy.’ According to the FDA’s website, this rare status “is intended to expedite the development and review of drugs for serious or life-threatening conditions.” It is given only when early clinical evidence demonstrates that a therapy “may have substantial improvement on at least one clinically significant endpoint over available therapy.” Since decades have passed without much progress in the treatment of urothelial bladder cancer, and since another 74,000 Americans will be diagnosed with bladder cancer in 2014, breakthrough therapies are desperately needed for this disease.

MPDL3280A is one of several anti-PD1 therapies designed to silence the false signals that turn off the immune system’s radar and allow some cancers to grow. Other trials at Yale have found that anti-PD-1 therapies are effective against melanoma, kidney cancer, and non-small cell lung cancer. One of these drugs, nivolumab, was recently approved in Japan for treatment of melanoma. Like MPDL3280A, nivolumab works by thwarting PD-L1, which allows the immune system to switch back on and dramatically shrink tumors. The effects of the antibodies can be long-lasting; the therapies may cause the immune system to produce ‘memory lymphocytes’ that aren’t tricked by the cancer cells’ ‘false signals.’

Dr. Petrylak recently completed a Phase II trial on MPDL3280A at Yale, but can’t yet discuss the findings. He foresees most bladder cancer patients being treated with MPDL3280A in conjunction with chemotherapy. For patients who can’t tolerate chemotherapy, however, the new antibody could become a first-line treatment. “We need to sort out the factors that will lead to a response and give patients a durable response,” said Dr. Petrylak. Dr. Petrylak’s next step is to look for the optimal sequences and combination of therapies, including surgery, MPDL3280A, and chemotherapy. “We’re going to look at a variety of sequencing variables in the upcoming trials utilizing the antibody,” said Dr. Petrylak, “together with bringing in chemotherapy in the long- or short-term to improve outcomes.” He expects these trials to commence within a year.

“Immunotherapy,” he added, “is the most exciting area of genitourinary cancer research. I can see this becoming the standard of care at some point. It’s changing the whole field.”

[Image of Peter and Alaina Ehmer]