For decades, patients with the most common type of bladder cancer, urothelial carcinoma, had few treatment options. The standard chemotherapy for the disease contains platinum and is so toxic that many patients either refuse it or can’t tolerate the side effects. While two-thirds of patients see initial tumor response from chemotherapy, long-term benefit remains low at only 5 percent. The disease often spreads to other organs, bones, and lymph nodes. The National Cancer Institute estimates that 16,000 people will die from bladder cancer this year, with 77,000 new cases diagnosed.

But a new immunotherapy, tested in phase I and II trials at Smilow Cancer Hospital and other top cancer centers, has shown tremendous promise, significantly reducing tumors in some patients and completely eradicating them in others. The responses were not only dramatic but also prolonged. The results were so striking that in May the FDA approved the drug atezolizumab for patients with metastatic urothelial carcinoma that has not responded to platinum-based chemotherapy.

“The significance of these findings is that for the first time we’re really seeing a major improvement in tumor shrinkage,” said Daniel Petrylak, MD, Professor of Medicine and Urology and one of the lead investigators of the Yale trials. “About a quarter of the patients respond to atezolizumab, and when they respond, they usually respond for a long period of time. So it’s a major breakthrough.”

Atezolizumab is among a new class of immunotherapy drugs called “checkpoint inhibitors.” They block signals that cancer cells send to disable the immune system, which allow tumors to grow. Atezolizumab targets
a protein called PD-L1 (programmed death ligand 1) expressed by some bladder cancer cells. PD-L1 binds to the surface of bladder cancer cells and sends out chemical signals that switch off the immune system, opening the way for cancer cells to proliferate. When atezolizumab prevents PD-L1 from doing this, the immune system turns back on, detects the cancer, and attacks it.

The phase I trial at Yale was limited to just a small number of patients. But bladder cancer patients had not responded to platinum-based chemotherapy. The phase II trial included patients both with and without the biomarker PD-L1, though the presence of PD-L1 didn’t guarantee a patient’s response, it greatly increased their likelihood of responding – about 27 percent of such patients responded strongly to the drug. On the other hand, the absence of the biomarker didn’t completely exclude the possibility of a response – the drug also shrank tumors in 85 percent of patients who were negative for PD-L1.

The trials demonstrated beyond a doubt that non-bladder cancer patients with the PD-L1 biomarker, atezolizumab was a potent new option, an option long coveted. That’s why the FDA moved the drug through the process so rapidly, approving it just four years after the first trials began.

“This is not for all patients,” said Joseph W. Kim, MD, Assistant Professor of Medicine and one of the trial investigators at Yale. “It’s clear within the first two or three months if patients will benefit from the treatment or not. But for the patients who do well, their quality of life is remarkably better.”

One such patient is Dr. Gad J. Selig, 77, a dean in the University of Bridgeport’s School of Engineering. He was diagnosed with bladder cancer in 2008, and in 2012, the removal of his urethra and a kidney. Several types of chemotherapy didn’t help. “Some made me quite sick,” he said, “so I didn’t want to continue that route.” Then he heard about immune therapies and the trial at Yale. Though the treatment was experimental, he didn’t hesitate. “What other options did I have? You want to live, because you have kids and grandkids, and you do what you can.”

After testing positive for PD-L1, he joined the phase II trial in the summer of 2014 and started receiving treatments every three weeks. His tumors not only shrank, they disappeared, and his CT scans remain clean. He has felt only minor side effects, some arthritis that bothers him a bit when he plays racquetball and soccer. “Some people are less fortunate,” he said. “The treatment doesn’t work, and the cancer comes back.”

“That’s why it’s critically important that Smilow has access to these sorts of trials,” explained Dr. Kim, “so that we can offer promising novel therapies to our patients. Because in reality, if we didn’t have access to this drug, our patients would have no options.”

Yale was chosen for the trials for many reasons, said Dr. Selig’s physician, Joseph Paul Eder, MD, Professor of Medicine and another investigator on the trial. “First, we had the basic science investigators who have worked on this pathway since before its recognition in cancer. Second, we had clinical investigators with long experience dealing with immune therapies and the toxicities that occur with them. The drugmaker, Genentech, realized that Yale investigators and scientists know the science and know how to manage patients, so we were ready for this trial.”

The phase II trials also included patients who for various reasons weren’t eligible for platinum-based chemotherapy. Their survival rate was comparable to that of the overall group, a finding that will be tested more broadly in a phase III trial at Yale. If the results are confirmed, explained Dr. Petrylak, atezolizumab could become a first-line treatment for some people with bladder cancer, eliminating the terrible side effects of platinum-based chemotherapy.

The FDA approved atezolizumab only for patients who have failed at platinum-based chemotherapy and are PD-L1 positive, because the trials showed that the drug has a much higher chance of succeeding within that group. What about patients without the biomarker who think their last chance is atezolizumab?

“We don’t say, ‘Sorry, there’s nothing for you,’” said Dr. Eder. “We say, ‘We have other immune therapy trials looking at other ways of trying to enhance the immune response. You should go on those, and maybe we can improve your odds.’”

The PD-L1 pathway is only one of many, he added, and researchers have started to find others, such as B7-3 and B7-H3. They are also studying proteins such as OX40 that activate the immune response rather than inactivate it. “We’re also looking at targeted monoclonals that are showing really spectacular activity,” said Dr. Petrylak.

“In patients who either regressed or failed at atezolizumab, we’re seeing a 30 percent response rate.”

Trials that test combinations of drugs are also underway, such as atezolizumab with OX40, or atezolizumab with chemotherapy, or atezolizumab combined with other checkpoint inhibitors such as indolamine-2,3-dioxygenase inhibitor. Dr. Kim mentions an upcoming trial that will combine immunotherapy with a personalized cancer vaccine, made from patients’ own tumor cells.

“There’s no shortage of cutting-edge ideas about ways to enhance the immune response of patients who aren’t likely to do well on atezolizumab,” said Dr. Eder.

Researchers and clinicians at Yale never stop searching for new solutions to cancer. Clinical trials are crucial to this process. They also provide hope to patients such as Phyllis Vece. After being diagnosed with bladder cancer, Ms. Vece, now 85, had surgery on her ureter and bladder. Then the cancer moved into her lung. Dr. Kim said radiation and chemotherapy were inadvisable because of kidney problems, but he also told her about the atezolizumab trial. She joined in September 2014. The drug began shrinking her lung tumors. On her most recent CT scan, they were gone. She hasn’t noticed any side effects.

“I actually feel so good, it’s hard to imagine that I have cancer,” she said. “You know, just because you’re older doesn’t mean you want your life to end. It’s wonderful that I was able to see another great grandson born, and to go to my son’s 40th wedding anniversary party. I’m hoping that from what they learned from this trial, they can help more people.”

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