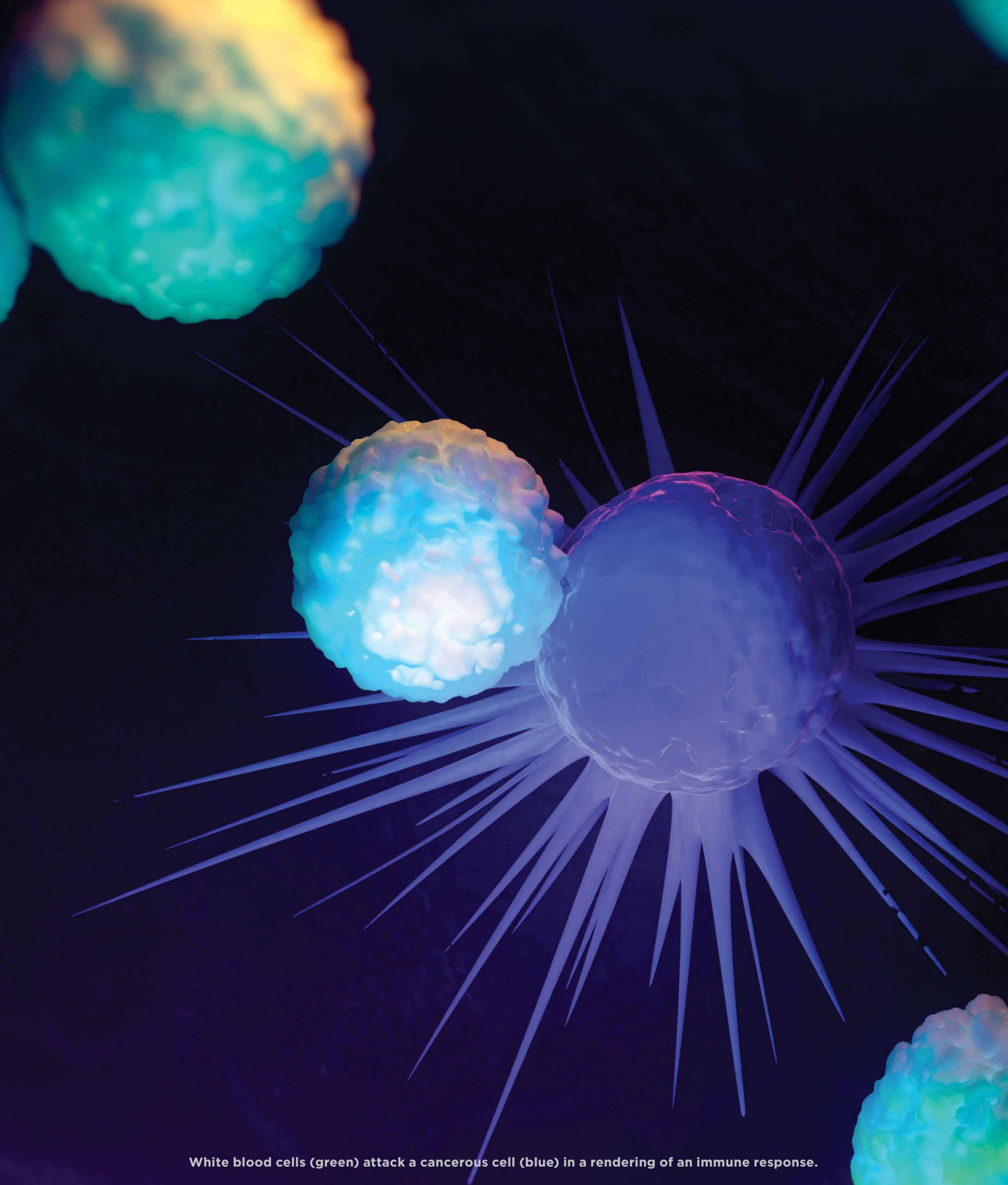


White blood cells (green) attack a cancerous cell (blue) in a rendering of an immune response.

TEACHING YOUR BODY TO KILL CANCER

Cure? Breakthrough? Revolution?

Uncommon words to be associated with cancer, one of the scariest diagnoses a patient can receive. Yet all those headlines, and many more like them, flashed around the world from Chicago in the first days of June as journalists reported on a new class of cancer treatments that were the stars of one of the world's largest medical meetings.

It is rare that the American Society of Clinical Oncology (ASCO) annual conference generates such upbeat headlines. Disappointing trial results and incremental advances are far more common, and skepticism the prevailing sentiment. Any talk of a "cure" is usually dismissed as hype by most cancer experts. This year, though, saw a discernible shift in tone as the meeting turned into a coming-out party for an emerging group of drugs known as immunotherapies, which harness the body's immune system to beat back malignancies.

The biggest news was a clinical trial testing a combination of two immunotherapies in 945 patients with advanced melanoma, the deadliest form of skin cancer. Both drugs are made by Bristol-Myers Squibb: Yervoy, approved in 2011, and Opdivo, approved last December. The disease was kept in check in patients on the combination for 11.5 months on average, compared with 2.9 months for patients receiving Yervoy alone, a significant improvement. Plus, close to 58 percent of patients saw their cancer improve on the combination, versus 19 percent on Yervoy alone. ➜

"IT IS ACTUALLY PLAUSIBLE THAT IN 10 YEARS WE WILL HAVE CURES AND THERAPIES FOR MOST, IF NOT ALL, HUMAN CANCERS."

—Gary Gilliland, President, Fred Hutchinson Cancer Research Center, Seattle

Those results are part of a wave of positive data coming out for immunotherapies tested against a broad variety of cancers, including liver, colon, breast, head and neck, and brain. One late-stage clinical trial of Opdivo against lung cancer, the biggest cancer killer, was so positive that lead researcher Dr. Luis Paz-Ares of Madrid described the results as a "milestone."

There have been breakthrough cancer treatments before, most notably the targeted therapies led by Novartis's Gleevec, approved in 2001 for chronic myeloid leukemia. Targeted therapies pinpoint cancer cells without harming healthy cells, so they usually carry fewer side effects than conventional chemotherapies, which flood the body with poison. But the immunotherapies go a step beyond the targeted drugs, by holding out the promise of lasting results.

Cancer cells almost always mutate to adapt to whatever poison is thrown at them, including targeted therapies, and the disease comes roaring back. Patients typically die not from the original cancer, but the recurrence. Immunotherapies may prevent relapses by priming the immune system to "remember" cancer cells if they re-emerge. Long-term follow-up of patients with late-stage melanoma treated with Yervoy found that 22 percent were alive at the three-year mark, and 17 percent were still alive after seven years.

It's those kinds of results that prompted Dr. Roy Herbst, chief of medical oncology at Yale Cancer Center, to use the word "spectacular" when discussing immunotherapy. "I think we are seeing a paradigm shift in the way oncology" is practiced, he told ASCO attendees. "The potential for long-term survival is there."

That's quite a statement, given that the vast majority of cancers are still treated much the way they were when President Nixon declared his "war on cancer" in 1971—with chemotherapy, radiation, surgery or a combination of the three. Though the survival rate for cancer patients five years after diagnosis now stands at 68 percent, almost 20 points higher than in 1980, cancer experts attribute most of that improvement to earlier and better diagnosis. Even the most successful new drugs can promise the sickest patients only several extra months of life on average.

Immunotherapies have their limitations. At this point only 8 percent to 40 percent of patients

respond to the drugs, and side effects can be severe. Three drug-related deaths occurred in the trial combining Yervoy and Opdivo, and a third of patients receiving the combination had to drop out because of side effects.

The biggest barrier to overcome, however, could be the cost. Yervoy, given in four infusions three weeks apart, costs $120,000 for a course of treatment. Opdivo, administered every two weeks, costs $150,000. Oncologists are alarmed that these prices will put these drugs out of reach of many cancer patients.

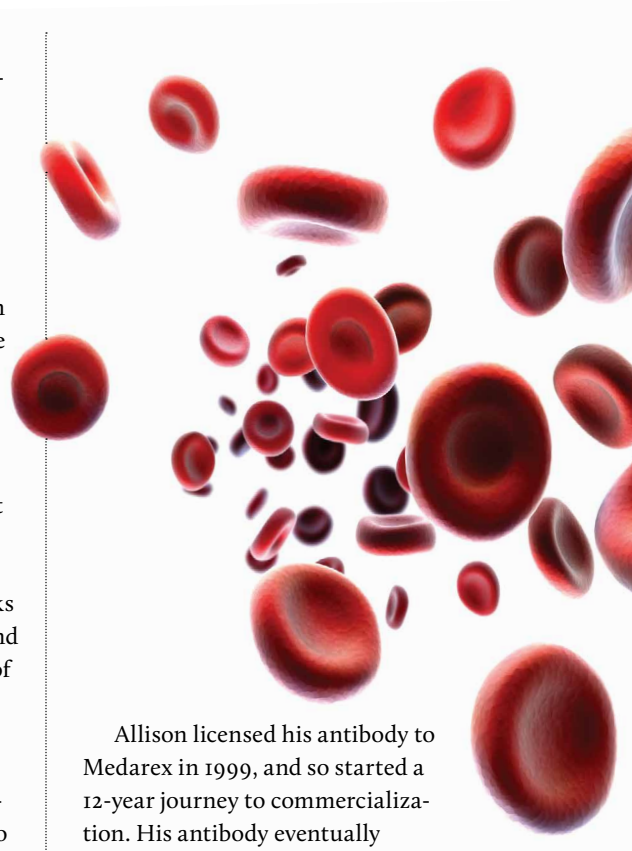
Nevertheless, immunotherapies are the most promising cancer treatments to come along in at least a decade. Decision Resources Group predicts the global market for this class of drugs will reach almost $9 billion in 2022, driven by the expected approval of nine new drugs. The director of the Food and Drug Administration's oncology division, Dr. Richard Pazdur, described immunotherapies as potentially "transformative" treatments capable of changing the course of patients' lives and has vowed to use the F.D.A.'s recently launched breakthrough-drug program to quickly shepherd the most promising candidates through the regulatory process. "We are in the middle of a revolution," said Dr. Louis Weiner, director of the Lombardi Comprehensive Cancer Center at Georgetown University. "I don't think that is hyperbolic. Those are the kinds of observations that we've rarely seen in our business."

"Breakthrough," however, may be an overstatement. Researchers have been working on immunotherapies for some 50 years; make that 120 years if you go back to the beginnings. That's how long scientists have been trying to figure out how to overcome the ability of proliferating cancer cells to evade and misdirect the body's immune system.

In the 1970s scientists discovered that a powerful component of the immune system, a white blood cell called a T cell, could be stimulated by proteins called interleukins. The resulting reaction destroyed malignant tumors. The race was on to clone interleukin proteins, and it was ultimately won by Chiron (now part of Novartis). Its interleukin drug, IL-2, won F.D.A. approval in 1992, first for kidney cancer and later for melanoma. IL-2 can produce remarkable results, but it only works for about 6 percent of patients, and side effects are brutal: 2 percent of patients die from the treatment.

The T cells stimulated by IL-2 act as a bludgeon against cancer; immunotherapies take a more nuanced approach. Over the past two decades scientists identified those components of the immune system that detect cancer cells, or prevent T cells from detecting them, and started working on drugs that would target those components.

The race to cure cancer is global. French researchers made one of the most significant discoveries in 1987 when they found a protein on the T cell's surface that acts as a brake on the immune system. The brake is called CTLA; 10 years later James Allison, then a professor at the University of California, Berkeley, and now chairman of the Department of Immunology at Houston's M.D. Anderson Cancer Center, developed an antibody that blocks CTLA, thus freeing the immune system to attack tumors. As he says, "we are treating the immune system, not the cancer."



Allison licensed his antibody to Medarex in 1999, and so started a 12-year journey to commercialization. His antibody eventually became Yervoy, approved in 2011 as the first of a new class of drugs called checkpoint inhibitors.

Medarex was purchased in 2009 by Bristol-Myers, its development partner, for $2 billion. The next year Bristol-Myers presented some attention-getting clinical trial results at ASCO: Although only 10 percent of advanced-stage melanoma patients responded to Yervoy, those patients who did survived four months longer than those receiving chemotherapy. More remarkably, about 25 percent of those responders were still alive two years after treatment, when their predicted survival had only been seven months. It was the first drug to increase survival for the sickest melanoma patients, and a review in the science journal *Nature* concluded that Yervoy "provides clear clinical validation for cancer immunotherapy."

A second checkpoint inhibitor from Merck, named Keytruda,

was approved by the F.D.A. in September 2014, followed by Bristol-Myers's Opdivo in December, both for malignant melanoma. Keytruda and Opdivo target a slightly different T-cell brake than Yervoy, known as PD-1, which is why Bristol-Myers decided to combine Yervoy and Opdivo in a clinical trial. By blocking two brakes, scientists figured they would hit the cancer cells with a one-two punch.

The PD-1 drugs have a higher patient response rate than Yervoy and may turn out to be effective against a broader range of cancers, especially lung cancer. The American Cancer Society predicts 221,200 new cases of lung cancer in the U.S. this year and 158,040 deaths, more than other cancer.

Opdivo was approved this March for squamous-cell lung cancer, which accounts for about one-quarter of all cases. The clinical trial reported at ASCO tested Opdivo against nonsquamous cell lung cancer, responsible for 70 percent of cases. Patients on Opdivo lived a median of 12.2 months, compared with 9.4 months for those receiving chemotherapy, a significant improvement for patients near death. Dr. Alan Worsley, Cancer Research UK's senior science information officer, told the BBC that "advances like these are giving real hope for lung cancer patients."

Some 30 checkpoint inhibitors are now in varying stages of development, and several have F.D.A. "breakthrough" status, which "fast tracks" the approval process. Also in the pipeline is a new class of immunotherapies that can be classified as highly personalized medicine. Called CAR Ts, (CAR is short for "chimeric antigen receptors") these drugs are made by extracting a patient's T cells from bone marrow, attaching a piece of an engineered virus, and then injecting the modified cells back into the patient where they can eliminate cancer cells.

Novartis formed an alliance with CAR T pioneers at the University of Pennsylvania in 2012 and gave the school $20 million to build a cell therapy center. In an early trial of the first drug to come out of the UPenn/Novartis alliance, 36 out of 39 children with acute lymphocytic leukemia had a complete remission, and 75 percent were alive six months later.

"IT'S POSSIBLE THAT WE'LL BE ABLE TO PINPOINT, IN ADVANCE, WHICH PATIENTS ARE THE BEST CANDIDATES FOR THESE THERAPIES."

—Dr. Lynn Schuchter

It's not just big pharma chasing CAR T. Several biotech start-ups are developing these drugs as well. The most notable is Seattle-based Juno Therapeutics, which raised $265 million in its initial public offering in December, just 16 months after its founding – one of the largest biotech IPOs ever. On June 30, 2015, biotech powerhouse Celgene paid $1 billion for a development partnership and 10 percent stake in Juno. Juno spun out of Seattle's Fred Hutchinson Cancer Research, and on the day the Celgene deal was announced, Fred Hutchinson's president, Dr. Gary Gilliland, told a meeting that "it is actually plausible that in 10 years we will have cures and therapies for most, if not all, human cancers." Stunning words coming from a cancer hospital president. Gilliland also acknowledged "the costs of oncology care are not sustainable."

Oncologists are not sure which patients will respond to which drug. This makes cancer difficult to treat, despite all of the new drugs. Drug companies are hoping to solve this problem by developing companion diagnostics to better match patients with drugs. For example, one small study tested for a particular defect in the DNA present in about 4 to 5 percent of tumor types. The study found 60 percent of colon cancer patients who tested positive for the defect responded to Merck's Keytruda – while zero patients without the defect responded. If diagnostic tests could be paired with each immunotherapy, the numbers of patients treated and the overall cost to the health care system could be far lower. This is a new avenue being pursued.

Plenty of cancer experts are optimistic that this will all work out. "The field of targeted immunotherapy gets more exciting every year," said Dr. Lynn Schuchter, head of the Hematology/Oncology Division at the University of Pennsylvania's Abramson Cancer Center. "We're rapidly moving past the era in which immunotherapies are seen as breakthroughs for melanoma alone. Remarkably, these drugs are proving effective in other cancers where practically no treatments work. Just as important, it's possible that we'll be able to pinpoint, in advance, which patients are the best candidates for these therapies." As these changes take place, oncologists might even begin using the word "cure" and no one will accuse them of hype.

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