Her chart said ‘two weeks to **fatal event.’**

Ten years later, she’s **still alive.**

Immunotherapy is saving lives in clinical trials. But as these powerful drugs are tested, not everyone gets a shot at a cure

BY ALICE PARK

When Stephanie Florence, pictured in March 2016 in her hometown of Lewiston, Idaho, took an immunotherapy-based drug, her lymphoma went into remission

PHOTOGRAPH BY CHARLEY ZHENG FOR TIME

Dates are important to a person who knows he's dying of cancer.

There's the day when he learned he was sick. There's the date of his first surgery, or of the first time a vein in his forearm was punctured with a tube full of poison. There are also those dates in the future—each one a temporal goalpost that represents hope when every day feels doubtful. For Mike Hindt, who was diagnosed two years ago with metastatic pancreatic cancer, that date was April 23, 2016.

That's when the first of his four children will get married, and despite his dismal prognosis, Hindt, 56, was determined to see his second oldest say his vows. The trouble was, Mike had run out of traditional treatment options. He had already had extensive surgery and been through nearly a dozen sessions of brutal chemotherapy. But pancreatic cancer spreads so quickly that it isn't usually diagnosed until it's entrenched in several internal organs. In Mike's case, it was his liver, and more of the status quo wasn't on the table.

Since his diagnosis, Mike's wife Veronica had made a full-time job of seeking treatment options for her husband. And as of last summer, when Mike's doctors said they had nothing else to offer him, Veronica knew they'd have to widen their search. She ventured into the world of experimental therapies, treatments that haven't been proven but are promising enough to be tested in people enrolled in clinical trials.

She canvassed experts, called up cancer centers and spent hours doing research online, where she learned about immunotherapy, a new approach to cancer that oncologists are calling the most promising in decades—and probably ever. Veronica read of an ongoing Duke University trial of a drug called pembrolizumab that is approved and used to treat melanoma and was showing early promise against cancers in other parts of the body too. It's the same drug that just a few months later would send former President Jimmy Carter's melanoma, which had spread to his brain, into remission seemingly overnight. In August 2015, Mike learned he'd been accepted into a trial for that same drug.

In principle, immunotherapy is simple. It's a way to trigger the immune system's ability to seek out and destroy invaders. That's how the body fights off bacteria and viruses. But it doesn't do that with cancer, which occurs when healthy cells mutate to outsmart those built-in defenses. That's where immunotherapy comes in. "Instead of using external forces, like a scalpel or radiation beams, it takes advantage of the body's own natural immune reaction against cancer," says Dr. Steven Rosenberg, an immunotherapy pioneer and chief of surgery and head of tumor immunology at the National Cancer Institute (NCI). These strategies don't target cancer itself but work on the body's ability to fight it. These therapies, administered in pill or IV form, trigger the immune system to fight cancer cells while keeping healthy cells intact. For someone as frail as Mike, that was an especially appealing prospect.

In the past decade, scientists have come closer to making a reality of immunotherapy's promise. Some trials of the latest generation of these therapies have already produced astounding results. In studies of people with certain types of B-cell leukemias and lymphomas who haven't responded to any other treatment, upwards of 80% of them have seen their cancer disappear. "It's unprecedented to see these kinds of results in such early trials," says Dr. Stanley Riddell, an immunotherapy researcher and oncologist working on one of those trials with his colleague Dr. Cameron Turtle at the Fred Hutchinson Cancer Research Center in Seattle.

Market experts estimate that in 10 years, immune-based treatments will generate anywhere from $35 billion to $70 billion a year in sales. That would make immunotherapy by far the most valuable class of medical drugs in history, eclipsing the current record holder, cholesterol drugs like statins. Immunotherapy, which Vice President Joe Biden says could be "revolutionary," is also central to the Obama Administration's new "moon shot" to cure cancer.

There are currently 3,400 immunotherapy trials under way in the U.S. and many more around the world. These trials are hoping to prove that immunotherapy is not only a safe but also a better way to battle certain cancers—one that may eventually spare people the life-sapping effects of chemotherapy and the years of follow-up surgeries.

But it also highlights the chasm between the fast pace of scientific progress and the ability to deliver it to the people who need it most. That makes the clash between the priorities of scientists, drug companies, regulators and patients unavoidable—at least for now. Scientists are barreling ahead, trying to make some of the most impressive drugs ever developed. Drug companies are bankrolling many of those studies in the hopes of bringing to market a revolutionary kind of medicine. And regulatory agencies, focused on safety and effectiveness, push for stringent testing criteria that may shut out many patients from early access to experimental drugs.

In the balance are the nearly 7 million people around the world who die of cancer every year. A handful of them may make it into trials and see miraculous results. Others have no choice but to wait.

The Question of Access

THE IMMUNOTHERAPY DRUG THAT worked for President Carter is the result of decades of frustrating fits and starts. Thirty years ago, this kind of treatment was "just a dream," says NCI's Rosenberg. While scientists have long been attracted by the notion of turning the body's own defenses against cancer, they hit roadblock after roadblock—the most basic being the fact that tumors arise from healthy cells gone rogue, so the immune system doesn't see them as foreign. That's why the first generation of immune drugs, antibodies against tumors, did not make as much of an impact as doctors had hoped.

Even so, it's not as if the immune defenses are completely useless when it comes to cancer. Killer immune cells do infiltrate malignant cells; doctors find them when they cut open tumors. But the immune system is no match for fast-growing cancers. It wasn't until Rosenberg showed that he could slow tumor development by activating the killer immune cells known as T cells to do their job more effectively that immunotherapy began to show promise. Still, the T-cell approach worked only about 15% to 20% of the time.

"We used to think that T-cell therapy was the safest thing in the world," says Turtle. "But that's probably because it didn't work very well." Most cancer patients still had to rely on surgery, chemotherapy and radiation. Then, in 1996, James Allison, then at the University of California, Berkeley, and now at MD Anderson in Houston, figured out how immune cells could be trained to identify and attack cancer cells. Killer T cells are actually restrained from targeting and destroying cancer cells, but by releasing this restraint, so-called checkpoint inhibitor drugs allow immune cells to attack the now exposed cancer cells—and not normal cells.

Yet testing such a new strategy carries formidable challenges. The question of who gets to try an unproven therapy is particularly loaded because of how good—how targeted—these new drugs are. Immunotherapy is largely ultra-personalized medicine, and it requires ultra-personalized trials. "It used to be that if you had lung cancer, you could find a clinical trial for people with advanced lung cancer," says Dr. Richard Schilsky, chief medical officer of the American Society of Clinical Oncology (ASCO). "Now, advanced lung cancer isn't enough. You have to have advanced adenocarcinoma lung cancer with an ALK mutation that only occurs in 2% of lung cancers."

This makes it nearly impossible for patients to find an appropriate clinical trial, discouraging all but the most stubborn—people like Mike Hindt, and people like Stephanie Florence. By her own admission, Florence, 44, a photographer living in Lewiston, Idaho, had to "bulldoze" her way into a trial by being persistent to the point of obnoxiousness. Diagnosed in 2006 with a form of lymphoma, she was told that her cancer was incurable and that only 1% to 2% of people don't relapse, even with chemotherapy and immune-cell transplants. "They didn't think chemo was going to save me," she says. "At one point, when I was in the exam room waiting for the doctor, I opened my chart and it said, 'Two weeks to fatal event.'"

After trying traditional treatments with no long-term success, she found a trial of a new approach, but it was for people with leukemia, not lymphoma. She still managed to wrangle a visit with the study's lead doctor, Dr. David Maloney, at the Fred Hutchinson Cancer Research Center. On the day of the meeting, she and her husband drove five hours from their home to meet him.

Maloney was getting ready to test the treatment in lymphoma patients, but Florence was still in remission from her previous treatment, an immune stem-cell transplant. Eager to join the trial, she followed up with several more visits, some of them unscheduled, and by sending every test result she got to Maloney's team. She called his office

COURTESY OF VERONICA HINDT

'We didn't know you could get booted out of a trial. We were blindsided.'

Veronica Hindt speaks of her husband Mike, pictured in 2010, before he was diagnosed with metastatic pancreatic cancer. He was dropped from an immune-based drug trial last summer.

repeatedly. When she didn't hear back, she called again.

"I won't treat patients until they have exhausted essentially all reasonable options," says Maloney. "In addition, all of our patients have to have active disease. These treatments are toxic, and it's not wise to get into clinical trials at the wrong time."

The irony was that Florence had to be sicker in order to qualify for the study; only after she was done with the standard treatment and her cancer returned, as she knew it inevitably would, did she become eligible for Maloney's trial.

The Phase 1 safety study was testing a type of immune therapy known as adoptive T-cell transfer. Doctors would extract Florence's blood cells and pick out cancer-fighting T cells that could recognize proteins in tumor cells. These would then be genetically modified to more specifically target proteins on her cancer. With the deck stacked with these killer cells, the chances that her immune system could overpower the tumor cells would be much higher. She would then get chemotherapy to eliminate as much of her existing cancer as possible, before doctors would give her a transfusion of those immune-enriched cells, which would repopulate throughout her body and attack her cancer.

Even though she had come to view it as the only way she wouldn't die before her 45th birthday, the guinea-pig element of the study gave her pause. Maloney's colleagues described the risks: fever high enough to put her in the hospital, hallucinations, coma, even death. "I started crying," says Florence. "I told my husband, 'I don't know if I'm doing the right thing.'" Because the study was among the first to test the treatment in people with lymphoma, the doctors could only guess at what the side effects could be. "It's like jumping off a cliff. I realized that there are no patients who are 10 years ahead of me that I can look to. That's me. I'm the one who is going to be that case."

Fortunately, Florence never experienced any of those side effects—not even a fever. For a while, she worried that meant the drug wasn't working. But after four weeks, she learned she was among the 80% to 90% of people in the trial who went into remission. "It was like my life started in that moment," she says.

IRINA ROZOVSKY FOR TIME

'I didn't want to die.'

Doris Ann Price has metastatic breast cancer. She's pictured in March 2016 in New Hampshire. She and her husband relocated from their home in North Carolina to the Boston area, where they are staying with a friend, in order to participate in an immune-based-drug trial. So far, she is improving.

The Clinical-Trial Quandary

THERE ARE REASONS SOME DOCTORS are wary of recommending clinical trials, even for treatments as promising as immunotherapy. On a practical level, most do not have the time to keep up with the thousands of studies undertaken by drug companies and the government, so they may not know what to recommend. Many are also unwilling to take on the responsibility of putting their patients on an untested treatment. The costs are also prohibitive; it is three to five times more expensive to care for a patient on a clinical trial because there are more tests and monitoring for side effects. And while many of the costs are covered by the trial, those of the patient's doctor are not. The more time doctors spend on patients in a clinical trial, the less time they have to see other patients whose care is reimbursed by insurers.

What many doctors do instead is refer patients to clinicaltrials.gov, a website launched with much fanfare in 2000, which was designed to list every trial of an experimental therapy being tested in the U.S. and more than 150 other countries. It provides contact information and details about which patients qualify for the studies, making it the default resource for anyone in that final phase of cancer care. But people who have used it complain that it's buggy, cumbersome and full of errors, including wrong phone numbers and inexact information about eligibility.

Even if a patient can find the right one, clinical trials are designed to answer scientific questions, not to provide subjects with an immediate cure. That's why trials have strict and specific criteria: people have to have a certain type of disease, at a certain stage, and show certain symptoms. And with the latest immunotherapy drugs, which aim to take a highly personalized approach to cancer, the eligibility criteria are narrowed even further.

The researchers, the drug companies and the Food and Drug Administration (FDA) all want to ensure that any changes in patients can be rightly attributed to the drug they're testing and not to something else the patients took before. Drug companies also have considerable control over whom they admit to their trials—and whom they reject—using those same eligibility criteria. Smaller companies, which have less funding to support large and lengthy trials, may prefer to keep the most responsive patients in their studies, so that the results look more favorable and their investment in the expensive studies pays off. Their ultimate goal, of course, is FDA approval for their product.

Clinical trials are designed to answer scientific questions, not to provide an immediate cure

Still, even with those patient-unfriendly pressures, Mike Hindt's wife Veronica was certain the trial was her husband's only chance at survival. She's probably right, but the promise of immunotherapy also brings with it a sobering reality: since it's still unproven, not everyone with untreatable cancer gets to try the drugs. There aren't enough spots in these studies for everyone who could possibly qualify for them, and people who do qualify may have to move to participate. And even those like Mike, who get into trials in their home states, can be removed if they don't continue to meet the rigid parameters. It's the kind of caveat that's right there on the consent forms, but it's not the kind of caveat that hopeful—and terminally ill—people think will ever apply to them.

"Mike felt wonderful on the pembro," says Veronica of his experience with the immunotherapy-based drug. "He was doing really well." But then, six weeks after he was enrolled, Mike was dropped from the trial. Veronica says he hadn't had any bad reactions at the time he was taken off the drug. His doctors say his liver lesions were still growing too fast, beyond what was allowed by the study protocol. That meant, according to Duke and Acerta Pharma, the company sponsoring the study, that he no longer qualified for the trial. "We didn't know you could get booted out of a trial," says Veronica. "We were blindsided."

It was an especially difficult setback when the Hindts saw how successful the same drug had been for Carter. While it was approved in 2014 for the type of cancer Carter has, there still aren't studies showing that it can help in cases where the cancer has spread to the brain, as it had with him.

Dr. Niharika Mettu, one of the Duke study's investigators, says the immunotherapy drug Mike was taking poses a unique problem in assessing how well it is working, because it can cause some cancers to temporarily look worse, as clusters of immune cells flood a tumor. Since Mike was removed from the trial early, it's impossible to know if that would have happened to him. About 30% of people taking this type of immunotherapy end up in remission. That's where the process of clinical trials can backfire for some patients who are sick today. These studies focus on the future, and their purpose is to produce the best new therapies—not necessarily for patients who are diagnosed now, but for those who might be in coming years.

Some experts say there are other factors that can determine clinical-trial enrollment. The model for drug development has changed, and as treatments become more individualized, especially in cancer, manufacturers are focusing less on pursuing blockbuster medications that millions will take for a short period of time and turning their efforts instead to developing more tailored therapies for a smaller group of patients who will use a drug for many years. Under that model, drugmakers recognize that "the impact of their drug will be much greater if they have a way to preselect patients for trials," says ASCO's Schilsky—patients, in other words, who are poised to have the best responses to the medication.

This raises a question as important as it is unanswerable: How does one marry patients' hopes of being helped by an unproven drug with the scientific and financial requirements of researchers and drug companies?

"It's hard," says Dr. Michael Neuss, chief medical officer at Vanderbilt-Ingram Cancer Center. "There are competing goals and a lot of tension in that discussion. I've been doing this a long time, and I'm not sure how you do it the right way."

The Trial Doesn't Come to You

DORIS ANN PRICE, A 69-year-old real estate agent, was told by her doctors last year that she was out of options after various drugs had failed to contain the breast cancer that had spread to her lymph nodes, brain, lungs, liver and bones. Searching for a second opinion, she looked up her first breast oncologist, who, as it turned out, was conducting a trial at Dana Farber Cancer Institute testing a new way to optimize antibody-based treatment to control metastatic breast cancer. Even though the trial was in Boston and she lived in Raleigh, N.C., Price asked if she stood a chance at getting in. "I didn't want to die," she says, her voice high-pitched from the tumors that press on her larynx, straining her vocal cords.

When she found out she was a candidate for a new trial, she also learned another hard truth: trials don't come to patients. Patients have to go to the trials.

In August, she and her husband drove from Raleigh to Boston, despite having no place to stay. After a week in a hotel room paid for by their daughter, they wrote about their circumstances on a community blog. Several people in the area offered the couple rent-free housing during Price's treatment. In order to pay for food and other expenses, the couple are trying to sell their home, and Price's husband, laid off from his job at IBM, took a couple of part-time shifts a week at the outdoor-apparel store REI. The Prices have also turned to GoFundMe, the crowdfunding website, to solicit donations to help them make ends meet.

So far, Price says, the sacrifice has been worth it. She's responding to the treatment, and her doctor says that if it doesn't control the spread of her cancer enough, she can move on to another study. It's trial and error, but it represents her only chance at survival. That kind of trial and error is also, critically, the only way science can work its way toward a cure.

"People are definitely talking about the *C* word," says Turtle of the term that, for good reason, makes oncologists squirm. "But there is no way anyone can say *right now* that these therapies are curative." Still, most experts agree the potential is there. Even if it's not technically a cure today, it's the closest scientists have come to it in a long time, maybe ever.

'I vowed to my children to leave no stone unturned.'

Veronica Hindt, second from left, is critical of the fact that her husband Mike was not able to continue taking a promising drug. She, Mike and their children are pictured at a pancreatic-cancer walk in 2015.

The Way Forward

AS WITH ANY MAJOR ADVANCE IN MEDICINE, the costs will be considerable. At the moment, treating a patient on a clinical trial with immune-based drugs, whether it's funded by the government or by a drug company, runs around $200,000 a year. That may be a drop in the bucket compared with some of the new cancer drugs that can cost double or triple that while extending life by just a few months. But it's hardly sustainable for treating the nearly 14 million people in the U.S. living with cancer. And although President Obama has pledged $1 billion to the national cancer-moon-shot effort, there's no indication of where that money will come from.

But since leading cancer experts predict that immune-based therapies may eventually replace chemotherapy, this research will likely find the investors it needs eventually. "I don't think that immunotherapies are going away," says Fred Hutchison's Riddell. "The results are just too good."

For now, people with certain lymph or blood cancers, like Florence, are benefiting most. These leukemia and lymphoma cancer cells have a distinguishing feature that scientists can already train immune cells to target. But researchers are thinking about how to move immune-based treatments to the biggest group of cancer patients—people who have the disease in their breast, colon, lungs or pancreas. Riddell suspects that if patients' immune systems are activated in just the right way—and early enough—they may be able to avoid chemotherapy and radiation altogether. Even for pancreatic cancer, there's hope that immunotherapy might one day reduce not only chemo but also the need for the extensive surgery.

For Mike Hindt, the results of those trials will come too late. In March of this year, a hospital in Georgia responded to Veronica's inquiries and offered to give Mike an experimental immunotherapy drug, off-label. That would mean he wouldn't be part of a study, and it could also mean he wouldn't be able to join future trials, since many don't allow any previous off-label-drug exposure. Mike and Veronica decided to go for it anyway. "I vowed to my children to leave no stone unturned in Mike's care," says Veronica.

But before they could make the 2½-hour drive from Charlotte to GRU Cancer Center in Georgia, and before he could give his son a bear hug and welcome his first daughter-in-law to the family, Mike passed away. The official cause of death was metastatic pancreatic cancer. ◻

COURTESY OF VERONICA HINDT