

# Cycle of a Drug Trial: Recovery and Relapse, Then Reinvention



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*Dr. Keith Flaherty with Christopher Nelson, a patient in his melanoma drug trial.*

By AMY HARMON

**O** n a sunny afternoon last June, Dr. Keith Flaherty stood before a large room packed with oncologists from around the world and described the extraordinary recovery of the melanoma patients in the experimental drug trial he was leading.

### TARGET CANCER The Next Hurdle

*Last of three articles.*

It was a moment he had looked forward to for months. Beyond a breakthrough for melanoma, the results were a promising sign for an approach to treatment for all forms of cancer that he and others had championed as more effective and less toxic than standard chemotherapy.

But even as he flashed the slide of his favorite graph, showing tumors shrinking in nearly every patient, his mind was

to dwell on what had happened to them since.

In the weeks leading up to the annual oncologists' conference here, several of the patients on the trial of the drug known as PLX4032 had relapsed. One had died. Another, Christopher Nelson, who had made what seemed like a miraculous recovery in March, had lost his appetite again. Dr. Flaherty feared what he might see on Mr. Nelson's scan when he returned to his office at the University of Pennsylvania.

The drug's ability to stop the melanoma, on average, he told the crowd, "appears to be approximately six months."

"I was hoping we'd get more time," said Dr. Grant McArthur, one of the six oncologists on the trial team, voicing the thought on everybody's mind when the group met at the conference. None of them had a financial stake in the drug.

Dr. Flaherty, whose perpetual optimism about this kind of treatment, known as targeted therapy, raised eyebrows among some colleagues, declined

to dwell on the drug's limitations. However briefly, PLX4032 had held off the cancer by blocking a particular protein in its cells that was spurring them to multiply. If such targeted drugs were ever to provide a lasting benefit, many oncologists believed they would need to be combined with others, much as cocktails of protease inhibitors have worked against H.I.V.

"We just need," Dr. Flaherty said, "to find the right combination."

If they acted quickly enough, they might even be able to help the trial's participants. Many were still in remission. Those who had relapsed were searching for another treatment, acutely aware that their time was running out: most melanoma patients die within a year after the cancer spreads.

The problem, which had bedeviled targeted therapies for other cancers, was that while PLX4032 blocked the protein made by one mutated gene, a second mutation now seemed to be driving the cancer's growth. If that mutation could be

## Stalling the Advance of a Deadly Cancer

Nearly all of the melanoma patients whose tumors carried a particular genetic mutation responded to an experimental drug, PLX4032, when it was given at a high enough dose. As of now, tumors of the 39 patients who responded in the drug's first human trial have stopped growing for nine months on average. Several patients are still in remission. Others have died, or are searching for another therapy.

### Those who responded to drug

ON TRIAL FOR AT LEAST 6 MONTHS



**Randy Williams,**  
Jonesboro,  
Ark.

Mr. Williams, 47, a contractor, has responded to the drug for 18 months. He drives 1,200 miles round trip to appointments in Houston to get his monthly quota of pills.



**Rita Quigley,**  
Huntsville,  
Ala.

Over the last 19 months, Ms. Quigley's initial tumors disappeared, but earlier this month new ones appeared in her brain and her heart. On Monday she started radiation treatment for the brain tumors.



**Mark Bunting,**  
Sandy,  
Utah

Mr. Bunting, 53, an airline pilot, told friends he was "leading the pack" when his tumors shrank by more than 80 percent. After relapsing, he is trying chemotherapy for a second time.



**Dezaerae Dittmar,**  
Marietta,  
Ga.

A tumor below her waistline, the size of a baseball, shrank to the size of a pea in the two months that she took the drug, but just as abruptly began to grow again. She died on Feb. 13 at age 46.



**Lee Reyes,**  
Fresno,  
Calif.

After months of using a feeding tube, Mr. Reyes began savoring food again after enrolling in the drug trial, but after a brief remission, his cancer came back. He died in September, 10 days after his 31st birthday.

### Did not respond

WITH MUTATION



WITHOUT MUTATION



Sources: ASCO 2009 presentation; New York Times reporting

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identified, they believed, its protein could also be blocked, in a game of biological Whac-a-Mole that just might be possible to win.

The most expedient approach would be to test PLX4032 in combination with other experimental drugs that targeted other mutations, including those seen in Dr. Flaherty's relapsing patients.

But a drug that gave a patient even a few months of life could generate billions in revenue. And the standard practice among pharmaceutical companies, which say they typically invest nearly a billion dollars developing and testing a single drug, is to get each drug approved individually before testing it with others, especially those of competitors that are still experimental. Even small Phase 1 trials can cost over a million dollars. And one drug that was safe and effective, they worried, might be tainted by association with another that proved to have toxic side effects.

As Roche, the pharmaceutical giant that had licensed PLX4032, made plans to test the drug in larger trials in hopes of quick Food and Drug Administration approval, Dr. Flaherty's colleagues in the laboratory would search for the new mutation in the tumor samples of patients who had relapsed, trying to understand why the drug had stopped working.

For his part, the doctor would try to keep his patients alive. And he would work to convince the pharmaceutical industry that the fastest path to finding a combination that really worked would require changing their standard operating procedure.

### A Bitter Pill

At 4:40 p.m. June 25, Mr. Nelson, 43, waited with his wife, Sharlene, in the melanoma clinic at Penn. Dr. Flaherty was running late.

Mr. Nelson credited Dr. Flaherty with snatching him from the jaws of death four months earlier. The name of the protein fueling his cancer had become part of his personal lexicon: it was called B-RAF, he told his poker buddies. Mrs. Nelson had recounted dozens of times the story of his turnaround on the Roche drug that blocked it.

"It's a miracle drug," she would say.

They sat side by side. To pass the time, Mr. Nelson tried to remember all the adjectives their 10-year-old daughter, Julia, had come up with for her Father's Day card the week before, each starting with one of the letters in "Christopher."

"C" was for caring, "H" was for helpful. "E" was for 'elderly person,' Mr. Nelson recalled. "I'm like, 'Thanks.'"

As he finished with other patients, Dr.

Flaherty found himself rehearsing what to say to the Nelsons. He relayed bad news almost daily; it was part of his job. But this, somehow, was worse.

When he arrived, he sat and faced them, meeting Mr. Nelson's eyes.

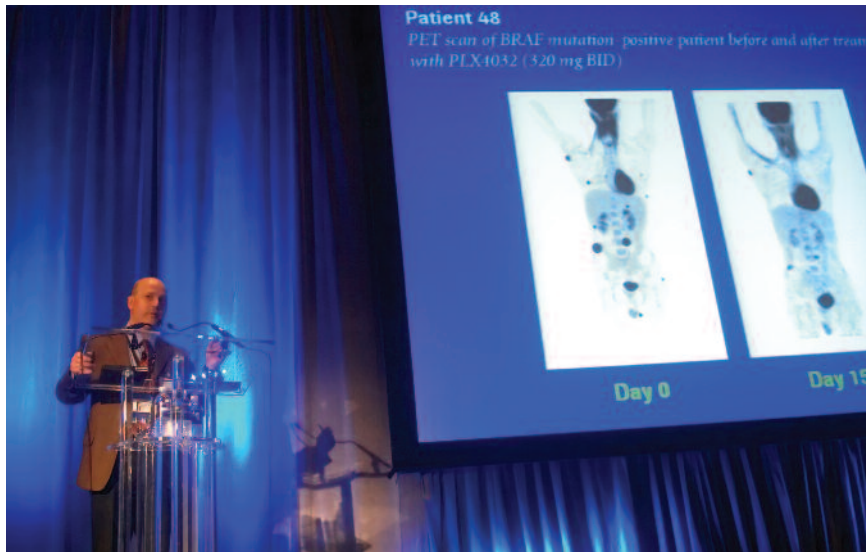
"The cancer," he said, "is starting to wake up again."

Mr. Nelson, always ready with a quip, said nothing.

"But this drug," Mrs. Nelson started, her voice breaking. "This drug could push it back just in the first two weeks — you would think it would just keep pushing!"

Then Dr. Flaherty gave them a new hope. One theory, he told them, was that the mutant B-RAF protein was managing to activate another protein on the same pathway in the cancer's cells. And a space was about to open up in the trial of a new drug designed to block the second protein.

Its developer, GlaxoSmithKline, required Mr. Nelson to wait at least a month to clear his system of the Roche medication. And Dr. Flaherty himself was moving to Boston the next month, where he would oversee targeted therapy development across all cancer types at Massachusetts General Hospital at Harvard. He was entrusting Mr. Nelson's care to a colleague, and would be in close touch.



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### OFFERING HOPE

Dr. Keith Flaherty, the lead investigator in a melanoma drug trial, discussing results at a conference last year.



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### FACING REALITY

Dr. Flaherty with Christopher and Sharlene Nelson. Mr. Nelson quickly recovered on the trial, enjoying a trip to the Jersey Shore. After a relapse, then new treatment and another lift, he told his wife in November: "I'm happy, Sharl. But how long do you think it will last?" He died last month.

Mrs. Nelson took her husband's hand. "O.K.," she said. "We have a plan."

### Pressuring the Industry

He had done his best for the Nelsons, Dr. Flaherty thought as he hailed a cab to the airport that evening to fly to Chicago, where he would give a talk on targeted therapy.

But over dinner alone near his hotel, he second-guessed himself. What if Mr. Nelson's cancer was not being fueled by the protein the Glaxo drug was trying to block? There were other likely drivers, which lay on a different pathway. And many cancer biologists suspected that both pathways needed to be blocked to stamp out the melanoma.

What bothered him more than anything was that he had to guess. The scientists studying the tumor samples were

proceeding slowly. Without the cooperation of the drug companies, it was impossible to know which was the best therapy for his patient.

Even if some combination of targeted drugs could put melanoma into a long hibernation — and that was still not clear, he knew — it might take a cocktail of five or more such drugs to treat any given case. And it can take 10 years for even one drug to reach the market.

"If they do it the way they've always done it," Dr. Flaherty complained in e-mail messages and calls to colleagues, "it will delay by years how quickly we can figure this out."

Such frustration, he knew, went beyond melanoma specialists, especially as it grew clear that there were so many new targeted drugs to be tested and that no single one was likely to hold off any given cancer for more than a limited time.

Unable to obtain drugs from the companies themselves, some researchers were paying to have the equivalent of designer knockoffs made so they could test the most logical combinations in laboratory animals. One such experiment had arrested the growth of lung cancer in mice, and clinical researchers were "climbing the walls," a colleague told him, because the companies who owned the two drugs had no plans yet to combine them in a human trial.

Over the summer, Dr. Flaherty urged the leading melanoma researchers to form an alliance to make it easier and cheaper for drug companies to conduct several trials at one time, advising them

which were the most promising.

Years earlier, he had secured the backing of a patient advocacy group, the Melanoma Research Foundation, for the idea. Forging cooperation among academic researchers had been more difficult, given that they compete for jobs and grant money. And many still believed that a different approach, which boosted patients' immune systems, was more likely to produce a cure.

But the results of the PLX4032 trial offered the most substantial support to date for the targeted approach in an aggressive and common cancer. For many oncologists, it seemed to add a moral imperative to the demand for swift testing of the drugs in combination. And on a steamy morning in August, leading melanoma researchers from across the country gathered at a meeting in Boston to discuss it.

"This is the most important meeting for melanoma patients that's happened in years," said Dr. Lynn Schuchter, chief of oncology at the University of Pennsylvania.

The stories of those who had recovered and relapsed on the Roche drug gave the meeting its momentum. An avid golfer in New Jersey had played three rounds in the rain when the tumor under his arm receded enough to let him swing a club. One woman, 30, who had been told before joining the trial that she should "focus on the quality, not the quantity" of her days, was informed that her scans were cancer-free.

The average time the drug halted tumor growth had stretched to almost nine months. Yet Mark Bunting, the airline pilot who had once declared himself the trial's "leader of the pack," had been rushed into emergency surgery when a new tumor had pierced his bowel. And Mr. Nelson's initiation to the Glaxo trial had been delayed while he received radiation for tumors that had appeared in his brain.

The doctors agreed to hammer out the legalities of pooling resources among institutions, and Dr. Flaherty agreed to approach the companies on behalf of the alliance.

Their first choice would be to test Roche's B-RAF drug with another one the company owned. Glaxo had two drugs designed to block the same proteins. Novartis, Pfizer and Bristol-Myers Squibb also had drugs that might work best with a competitor's. If they had needed any more incentive, the doctors were increasingly urged on by the frustrations of their patients.

"Why can't they put them together and do it in one shot?" Mrs. Nelson wanted to know when she and her husband arrived at Penn in early October to start the Glaxo trial. "Wouldn't that give him a better chance?"

Mr. Nelson's latest CT scan showed the cancer throughout his body. Twelve tumors, though inactive, remained in his

brain. Another protruded from his neck. Because of a concern that the drug could cause vision problems, he had been examined by an ophthalmologist.

"My eyes are perfect, by the way," he told his wife, trying to make light.

### **A Plea Rejected**

Dr. Flaherty could tell by whom Roche sent to his first meeting with the company that he would make little headway. Any strategic decisions, he knew, would be made at a higher level.

Over sandwiches in a Midtown Manhattan office, a Roche official told him that the best interest of patients would be served by getting its B-RAF drug approved for sale as quickly as possible. "That has to be our focus right now," she insisted.

The request by Dr. Meenhard Herlyn, a prominent melanoma research scientist, to conduct preliminary tests of the drugs in the laboratory met with the same response.

"You know," Dr. Flaherty said finally, "other companies will be ready to do this."

But his habitual breakneck pace was

slower as he walked toward Pennsylvania Station with Dr. Herlyn, who had traveled from Philadelphia.

"That was a waste," Dr. Herlyn said flatly. As they parted ways, Dr. Flaherty, for once, was at a loss for a more positive spin.

### **A Death in the Family**

At an appointment in mid-November, the tumors on Mr. Nelson's neck and inside his heart had shrunk. "Aren't you excited?" Mrs. Nelson crowed.

Maybe, Mr. Nelson thought, he could make it to a poker tournament the next month after all. Or to his son's 17th birthday on Jan. 18. Or maybe not.

"I'm happy, Sharl," he said slowly. "But how long do you think it will last?"

A few weeks later, when Dr. Flaherty again made the pitch for a combination trial, this time at a meeting with Glaxo, an executive hinted that the company would sponsor such a trial soon. The company had a pragmatic reason: Roche was likely to get its B-RAF drug approved first, but Glaxo might take the lead if it had a combination that could do a better job. It was becoming clearer

that some targeted drugs might find a market only if combined.

"The culture is changing," the Glaxo executive agreed.

It would be too late, however, for Mr. Nelson. On Jan. 5, Mrs. Nelson wheeled him on a stretcher to his appointment at Penn. Three days later, an ambulance took him to hospice at a local hospital.

"Take me to Atlantic City instead," Mr. Nelson joked with the driver. "I'll pay you extra."

At his wake, Mrs. Nelson told relatives she felt blessed that he had lived longer than expected. They had celebrated their 21st wedding anniversary. With the children, he had ridden every water ride at Six Flags Great Adventure.

"It's a year I would never trade in," she said.

One year, Dr. Flaherty thought, when he heard the news. Certainly no triumph. But it was something. Something to be built on.

Novartis and Bristol-Myers had agreed to schedule teleconferences for later in the month to talk about combination trials. He checked the dates on his electronic calendar. A meeting with Pfizer was also pending.