Dr. Paul Nghiem originally had no interest in specializing in an extremely rare cancer.

In 2000, when Nghiem was a newly-minted dermatology resident working in Boston, he had seen exactly one patient with the skin cancer, known as Merkel cell carcinoma. But the disease was (and is) so uncommon — afflicting only 1,500 people per year in the U.S. — that Nghiem’s senior professor talked him into writing a textbook chapter on the cancer based on that sole patient encounter.

A resident who’d seen one patient “was somebody who knew a lot about it, compared to most [doctors],” said Nghiem. “I’m obviously making a joke, because I knew virtually nothing.”

In the 15 years since, Nghiem has thrown himself into everything Merkel cell, developing a career as a skin cancer researcher at the University of Washington (where he recently became head of the dermatology department) and Fred Hutchinson Cancer Research Center, as well as seeing patients with skin cancers at Seattle Cancer Care Alliance. Now, his clinical and research team’s efforts are starting to pay off.

At the European Cancer Congress held in late September in Vienna, Nghiem presented promising, early results from a clinical trial he leads based at seven sites around the U.S. testing an immunotherapy drug known as pembrolizumab (brand-name Keytruda) for patients with advanced Merkel cell carcinoma.

In part because this skin cancer is so uncommon, there are no targeted therapies available, Nghiem said. But such treatments are sorely needed — patients with Merkel cell carcinoma are about three times more likely to die of their disease than those with the better-known deadly skin cancer melanoma.

Instead, doctors have cobbled together treatments used for other cancers. Unfortunately, these therapies don’t work very well. For most patients with metastatic Merkel cell carcinoma (cancer that has spread to other parts of the body), their tumors start growing again within three months of starting conventional treatments.

Ten out of the 14 patients Nghiem and his colleagues have evaluated so far are responding to the drug — a vast improvement over currently available therapies for the cancer when it’s in advanced stages.
A skin cancer not like other skin cancers

It’s been an interesting road for Nghiem, from his first encounter with a Merkel cell tumor as a dermatology resident to becoming a specialist on the rare disease — and leading studies that could spawn the cancer’s first FDA-approved targeted treatment.

When Nghiem went to medical school in the early 1990s, the cancer was never even mentioned. The dermatologist was not enthusiastic about the textbook assignment at first, he said, but when he started reading the scant literature on the cancer, he became more and more fascinated.

The cancer is made up of cells similar to the type of skin cells known as Merkel cells. Like the cancer itself, Merkel cells are mysterious. Researchers have shown they are important for sensing gentle touch, but nobody’s quite sure of all of their functions.

Although most patients with this cancer have a normal immune system, it is more likely to strike people with a compromised immune system, like those who have received a heart or kidney transplant, or who are HIV-positive.

And unlike melanoma and other skin cancers, surgery is not as effective against Merkel cell carcinoma. Even if the tumor is removed with what seems like “clean margins,” Nghiem said, it may still recur an inch or two away.

“It doesn’t grow like a ball [like other skin cancers], it jumps,” Nghiem said.

In 2008, scientists at the University of Pittsburgh discovered a brand new virus inside tumors from eight out of 10 people with Merkel cell carcinoma. Dubbed the Merkel cell polyomavirus, this infectious agent turned out to be incredibly common.

In most people, the polyomavirus lives a benign life on our skin, starting from childhood. But sometime during the life of about 1 out of every 3,000 people, the virus, in combination with ultraviolet light exposure, age and bad luck will spur a Merkel cell carcinoma.

For Nghiem, who had recently moved his lab from Boston to Seattle, the virus’ discovery further flamed his interest in Merkel cell carcinoma. It was becoming exceedingly clear that the immune system would play an important role in the disease.

Immune cells vs. Merkel

In 2008, Nghiem teamed up with UW and Fred Hutch virologist Dr. David Koelle, an expert in how immune cells known as T cells respond to viruses in the skin. Together, the researchers studied the role of these cells in Merkel cell carcinoma.
Looking at several hundred patients, Dr. Kelly Paulson, at the time a graduate and medical student working with Nghiem, found that they were roughly divided into two camps — those whose tumors were swarming with a certain kind of killer T cells and those whose cancers were devoid of those cells. Patients who were able to send these immune fighters into the heart of the tumor fared much better, Nghiem said.

“When the T cells had gotten into the cancer, no one died,” he said.

Lack of T cells in the tumor did not mean patients would die of their disease, the researchers found, but there was a very strong correlation between T cells in the cancer and survival, “much stronger than in most cancers,” Nghiem said. “It was really obvious that an appropriate immune response could help someone survive this cancer.”

That finding, and later studies showing that patients often had T cells that recognize the Merkel cell polyomavirus, led the team to believe the skin cancer might be a prime candidate for immunotherapy.

Immunotherapies, or treatments that harness the body’s own immune system to better recognize and attack cancerous cells, hold promise for many cancer types — but some cancers may be particularly sensitive to this type of treatment.

Nghiem joined with Fred Hutch’s Dr. Mac Cheever, who leads the Cancer Immunotherapy Trials Network, to set up the pembrolizumab trial.

The researchers had reason to believe that drug could help even those patients whose T cells don’t track to their tumor, Nghiem said, as well as those whose immune cells were already attacking the cancer.

Many patients with Merkel cell carcinoma had “exhausted” T cells, meaning that even though the cells could recognize the cancer-causing polyomavirus, they could no longer effectively attack the tumor. Pembrolizumab and related immunotherapy drugs work by reversing such T cell exhaustion.

The immunotherapy trial is still in very early days — only 14 out of the 24 patients with metastatic Merkel cell carcinoma enrolled in the trial have had one or more scans after starting the drug. All 24 patients in the trial are given the drug every three weeks for up to two years and the researchers take CT scans every nine to 12 weeks to check the status of their tumors.

Based on the initial results, the researchers have seen that 71 percent of patients responded to the drug, and that each responding patient has continued to control the cancer’s spread for more than three months.

In comparison, about half of patients who were treated with only chemotherapy for advanced versions of this cancer saw their tumors grow after three months. That number jumped to 90 percent after 10 months, Nghiem said.
Some of the patients in the trial are six months out from starting on the drug and still doing well. They should have data from the remaining 10 patients in the study by early 2016, Nghiem said.

He’s especially encouraged by two patients who had to drop out of the trial early because the drug had some toxic side effects. One of these patients received only one dose of pembrolizumab and one had two doses — but both responded and are still doing well, even several months after stopping the drug.

“[This] response rate is really high,” Nghiem said. And he’s optimistic that the patients who’ve responded to the drug will continue to do well. “When the immune system gets rid of cancer, you’re dealing with the right mechanism,” he said.

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