ALK-positive NSCLC—patient's story opens eyes

Anne Ford

September 2013—For good or bad, Matthew Hiznay seems to be an odds beater.

First, a minority of lung cancer patients have never smoked. He's one of them, having been diagnosed with late-stage non-small-cell lung cancer in August 2011. Obviously, that's the bad.

Second, only about five percent of NSCLCs express a rearrangement of the anaplastic lymphoma kinase (*ALK*) gene. Hiznay's is one of them. That's the very, very good.

That's because on literally the same day that Hiznay received his diagnosis, the FDA approved crizotinib, a tyrosine kinase inhibitor that has been found to produce an objective response rate of 61 percent for *ALK*-positive NSCLC (Camidge DR, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13[10]:1011–1019).

Matthew Hiznay: "I kind of view myself as the poster boy" for molecular genetics' role in cancer.

And for once, Hiznay is in the majority: His cancer responded quickly and dramatically to crizotinib. On Sept. 10, 2011, he took his first dose of the drug. Two months later to the day, scans revealed no traces of the disease.

"He had been at death's door, and he had just a dramatic response," says Raymond Tubbs, DO, professor of pathology and section head of molecular oncologic pathology in the Department of Molecular Pathology, Cleveland Clinic, and the pathologist who identified the *ALK* rearrangement in Hiznay's cancer that was susceptible to crizotinib.

But this story is more than the account of one lucky young man and one effective medication. It's also the tale of a pathology team that was able to alter a patient's treatment in a powerfully specific way—as well as the account of a patient who helped that team realize just how crucial their work can be.

When Hiznay developed a persistent cough in July 2011, he assumed at first that it was related to his seasonal allergies. The busy 26-year-old, who had just completed his first year of medical school at the University of Toledo, decided to wait until the following month to have it checked out during his annual physical. That's when an x-ray revealed a hazy left lung and an initial diagnosis of sarcoidosis.

Shortly afterward, he discovered a rapidly growing knot in his left trapezius muscle, which led to the correct diagnosis—stage IV lung adenocarcinoma—on Aug. 26. As he learned, the primary tumor was growing in his left lower lobe, and it had metastasized to his right lung, all mediastinal lymph nodes, lower cervical lymph nodes, sternum, and gastrohepatic ligament.

For treatment, Hiznay headed to the Cleveland Clinic, where he received two pieces of good news. First, the cancer had not spread to his brain. Second, the director of the lung cancer medical oncology program, Nathan Pennell, MD, PhD, was sending a biopsy of the cancer for molecular genetic testing, "because," Hiznay remembers, "there were some new chemotherapy drugs coming on the market that were very specific for gene mutations. That was the first I'd heard about it. I didn't realize they could target a specific mutation like that."

Hiznay didn't expect the genetic testing to yield anything useful. "So much had gone wrong up to that point that I thought it'd be too good to be true," he says. "I wasn't getting my hopes up. I thought: I've already defied the odds by getting lung cancer without being a smoker, so how am I going to be able to defy the odds twice?"

Besides, there was a new and sinister development to deal with. The tumor had begun to slither around his pericardium, eventually leading to cardiomegaly, bilateral pleural effusion, bilateral collapsed lower lobes, a collapsed right middle lobe, pneumonia, a massive clot in his superior vena cava, pulmonary embolisms in both lungs—and, on Sept. 2, 2011, cardiac arrest. Hiznay's physicians considered a pericardial window to ease the stress on his heart, but by this point, Hiznay was so ill they feared he might not survive the procedure.

Dr. Tubbs

That was the state of affairs one week later, when Dr. Tubbs looked at the results of Hiznay's Abbott Molecular Vysis *ALK* Break Apart FISH assay (the companion diagnostic test to crizotinib) and realized something wonderful: Unlike almost all non-small-cell lung cancers, Hiznay's expressed a rearrangement of the *ALK* gene. "This is a fairly rare event," Dr. Tubbs says in his understated way. "I remember having the desire to tell the clinician as soon as possible, because Nate [Dr. Pennell] had let us know that this patient was really sick. The fact that I was able to give news that led to very specific therapy was exhilarating. That doesn't happen too often in pathology."

It took some time for the still very ill Hiznay to understand just how good the news was. "I remember I was still pretty out of it, but I realized it was good because the doctors who came in all had very excited smiles," he says. "I remember the doctor who took care of me in the ICU said, 'Congratulations. You're a mutant.' But I didn't grasp right away how important it was."

Because the FDA had just approved crizotinib on Aug. 26—the same day Hiznay received his diagnosis—the Cleveland Clinic had none of it on hand. A supply was shipped overnight, and Hiznay took his first dose on Sept. 10, becoming the Cleveland Clinic's first patient to take it outside of a clinical trial. One week later, he was well enough to leave the ICU for the solid tumor oncology floor. "And on Sept. 21, I was discharged, and I walked out on my own without any oxygen," he says. Two months later, a CT scan revealed no trace of cancer: "That was finally when I was really starting to feel well." Since then, crizotinib has been demonstrated to be superior to standard chemotherapy in patients with previously treated, advanced non–small-cell lung cancer with *ALK* rearrangement (Shaw AT, et al. Crizotinib versus chemotherapy in advanced *ALK*-positive lung cancer. *N Engl J Med* 2013; 368:2385–2394).

As good as he felt during his crizotinib treatment, Hiznay knew his tumor was likely to develop resistance to the drug. "I don't think anyone ever said it out loud to me, but I knew it was a possibility," he says. "That worry was definitely always there." Unfortunately, that fear became a reality in May 2012, when a biopsy of a swelling in his neck showed the cancer had returned.

Again a powerful drug was brought in to beat it back, this time an investigational compound from Novartis called LDK378, a second-generation ALK inhibitor that works in a similar manner as crizotinib. "It inhibits the ALK protein

much more strongly than crizotinib," Dr. Pennell says. "It's very promising for patients for whom crizotinib has stopped working." An 80 percent response rate for LDK378 in patients whose disease had progressed after treatment with crizotinib has been reported (Shaw A, et al. Results of a first-in-human phase I study of the ALK inhibitor LDK378 in advanced malignancies. Abstract No. 4400. 2012 European Society for Medical Oncology Annual Meeting, Vienna, Austria). At CAP TODAY press time, the first regulatory filing for LDK378 was expected to take place by early next year.

Hiznay received treatment with LDK378 through a clinical trial based at the University of Colorado Hospital, Aurora. As with crizotinib, he experienced quick and dramatic improvement. "I look forward to LDK378 getting on the market because it has even better results than crizotinib does for patients," he says. But for him, those results didn't hold. Seven months after the clinical trial, a PET scan showed his cancer was becoming resistant to LDK378.

"That is the reality of these new agents," Dr. Tubbs says. "The tumors learn to circumvent the action of the drug through other pathways. That's why there's intense research right now into understanding those mechanisms of resistance and developing ways to account for that resistance and circumvent it. The good thing is that there's new information coming out literally every week about acquired resistance and the mechanisms for potential therapeutic approaches."

Now that LDK378 is no longer efficacious against Hiznay's cancer, traditional intravenous chemotherapy seems to be doing the job. He began chemotherapy with bevacizumab, carboplatin, and pemetrexed last November, and in March a PET/CT scan showed that the cancer had again had a complete treatment response. Now on maintenance therapy, Hiznay hopes, of course, that the cancer won't return—but if it does, he says that yet more treatment possibilities remain. "I've never had targeted radiation therapy, so that would be an option," he says. A second round of crizotinib, in the hopes that the tumor has lost its resistance to that drug, is another possibility.

In the meantime, inspired by his own experience as a cancer patient, Hiznay has left medical school and enrolled in the Cleveland Clinic's molecular medicine PhD program, where he's studying the role of molecular genetics in cancer. "I kind of view myself as the poster boy," he says. By remarkable coincidence, one of his classmates, Hannah Picariello, worked on a clinical trial for crizotinib a few years ago. The two put together a presentation about Hiznay's experience, "It's Personal Now: the Future of Medical Research," which Dr. Tubbs invited them to give to the Clinic's molecular pathology department in May.

For listeners, the talk was a rare chance to hear firsthand how critical their work is. "There was a lot of emotion in the room from the people who do the testing," Dr. Tubbs recalls. "It's eye-opening whenever laboratory personnel hear patients discuss their illness, because we get so isolated in the laboratory. It's probably something we need to be more exposed to, so we never forget there's a patient who's going to receive the result that we are generating. We can never forget how important that is to them and their families."

Then, too, Dr. Tubbs himself found special meaning in Hiznay and Picariello's presentation. "Because I've had melanoma and prostate cancer, I had a perspective on his illness that I might not have had three years ago," he says.

For the moment, Hiznay is concentrating on his studies, undergoing maintenance chemotherapy every three weeks and CT scans every six weeks, and staying optimistic in his belief that the development of new treatment options will outpace his cancer. "It's very much a rapidly evolving treatment world," he says firmly. "You just have to stay ahead of the curve."

Anne Ford is a writer in Evanston, Ill.