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Novartis team perseveres to develop more personalized approach to breast cancer therapy.

By Elizabeth Dougherty | May 24, 2019

About a decade ago, after years of effort, researchers at Novartis had an experimental compound they thought might benefit cancer patients. They had a strong hunch, based on their research so far, that the cancer patients most likely to benefit had cancer with a mutation in a gene called PIK3CA, so they designed a clinical trial to test the drug in exactly those patients.

Back then, most cancer centers weren't equipped to sequence the genes of their patients' tumors and identify mutations. "This was very fancy at that time," says Cornelia Quadt, a clinical program leader in oncology at the Novartis Institutes for BioMedical Research (NIBR) who worked on the trial.

For decades, doctors had focused on the location of tumors in the body rather than the specific mutations spurring their growth. Oncologists were accustomed to treating tumors with radiation and chemotherapy. They often weren't prepared to identify patients who might benefit from a more targeted approach.

The Novartis team moved forward with their trial despite the challenge. Now after another ten years of research and development, the compound is approved for certain breast cancer patients with a PIK3CA mutation.

"This could be progress toward a more personalized approach in breast cancer," says Christine Fritsch, director of drug discovery biology at NIBR and a key member of the drug discovery team alongside scientist Michel Maira.

NIBR drug hunters and PI3K

When Novartis drug hunters were developing their first experimental PI3K inhibitors in the early 2000s, the PI3K pathway was on everyone's radar. It acts as a signaling hub in cells and is known to be active in many forms of cancer. The pathway receives messages from outside the cell and turns them into cues that trigger the cell to proliferate.

By 2006, Novartis researchers had already discovered two compounds that helped to inhibit the PI3K pathway and had one other in the works. Tests of all three investigational compounds in patients would later reveal that they acted too broadly and caused unwanted side effects.

Meanwhile, research in the field had uncovered a cancer-related gene mutation in PIK3CA, the gene that contains the instructions for building PI3K-alpha, one of four sub forms of the PI3K protein. PI3K-alpha regulates glucose metabolism, a process that turns sugar into energy.

The mutation flips the protein machinery on and drives cancer by giving cells a steady influx of fuel. "It becomes an accelerator of pro-survival, pro-growth signaling," says Francesco Hofmann, Global Head of Oncology Drug Discovery at NIBR.

It is possible to create many different small molecules that interfere with a given protein's activity, but not all are created equal. Novartis drug hunters synthesized and studied approximately 600 compounds that inhibited PI3K-alpha before homing in on one potential drug candidate. Image credit: Fidelis Onwubueke

In response to this new information, the Novartis researchers started a new hunt, this time for a compound that would predominantly inhibit PI3K-alpha. "We were constantly integrating what we were learning and informing the next wave of drug discovery," says Fritsch.

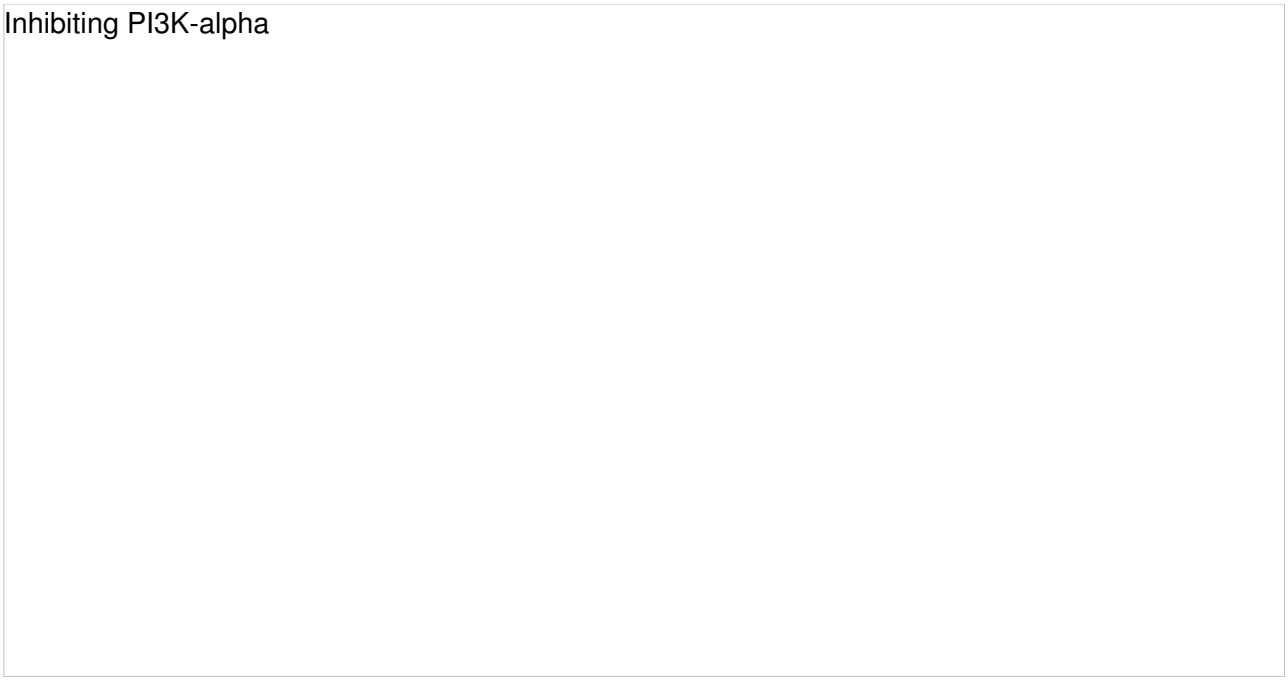
Advanced clinical trials

The Novartis team synthesized and studied approximately 600 compounds that inhibited PI3K-alpha before homing in on one potential drug candidate. Fritsch and her colleagues tested that investigational PI3K-alpha inhibitor using the Cancer Cell Line Encyclopedia, a collection of patient-derived cancer cell lines that had been genetically sequenced and categorized by Novartis and the Broad Institute of MIT and Harvard as part of a joint research program.

Tests against about 500 cell lines revealed that those most likely to die or stop growing when treated with the new compound had PIK3CA mutations.

It was this evidence that inspired the researchers to design a clinical trial to test the compound in patients with the PIK3CA mutation. The only way to do this was to sequence the tumor genes of every patient wishing to enroll.

Inhibiting PI3K-alpha



Novartis researchers started a hunt for a compound to inhibit PI3K-alpha when they learned that a mutation flips the protein's machinery on and drives cancer by giving cells a steady influx of food. Normally PI3K-alpha regulates glucose metabolism, a process that turns sugar into energy. When mutated, it becomes an accelerator of growth. Image credit: Alan Abrams

To get the trial going, the team worked with cancer hospitals that were already testing patients for gene mutations. Later, they set up a centralized screening solution so that they could include more patients from a wider variety of locations.

That early-stage trial revealed that patients with a few types of cancer, including breast cancer, responded to the drug. Other evidence, such as the Cancer Cell Line Encyclopedia tests, had also pointed to responses in breast cancer.

More cancer treatment findings for PI3K

Given the data from this study, the team felt they had enough evidence to invest in a late-stage trial of their investigational PI3K-alpha inhibitor in breast cancer patients with the mutation. At this point, however, the organization already had terminated development of three other investigational PI3K inhibitors.

"You can imagine that the organization was feeling some fatigue and skepticism," says Hofmann.

The team found additional instructive evidence in an unexpected place: an earlier failed Novartis trial that had run prior to discovery of the PIK3CA mutation. A close look at the data from that trial, which had tested an earlier investigational PI3K inhibitor in breast cancer patients, also showed a higher concentration of responses among patients with breast cancer with the mutation.

"You have to keep learning," says Hofmann. "Persistence and continuous learning are the keys to drug discovery."

The team zoomed in on patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer. Approximately 40% of patients with HR+/HER2- breast cancer have the PIK3CA mutation. Patients with the PIK3CA mutation may develop resistance to endocrine therapies. "There was an unmet medical need for HR+/HER2- advanced breast cancer patients with a PIK3CA mutation," says Fritsch.

The evidence taken all together allowed Novartis drug developers to design a clinical trial, which launched in 2015. US regulators recently approved the medicine, alpelisib, for use in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR+/HER2- advanced or metastatic breast cancer with a PIK3CA mutation, as detected by an FDA-approved test after disease progression following an endocrine-based regimen.

“This is a proud moment after so many years of false starts in both research and development,” says Tetiana Taran, Franchise Global Program Head for Breast Cancer in Novartis Global Drug Development. “Learning from multiple clinical trial experiences, we were able to advance a first of its kind targeted therapy for patients with HR+/HER2- advanced breast cancer harboring a PIK3CA mutation.”

> “If you want to be successful in drug discovery and bring forward a molecule, it needs persistence and it needs a continuous critical look at what you are doing and the ability to learn from it, even when things don’t go the right way. Don’t dismiss it. Don’t put it aside just like this. Try to apply your learning,” says Francesco Hofmann, Global Head of Oncology Drug Discovery at NIBR. Photo Credit: Laurids Jensen

Indication and Important Safety Information

PIQRAY® (alpelisib) tablets is a prescription medicine used in combination with the medicine fulvestrant to treat women who have gone through menopause and men who have hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer or breast cancer that has spread to other parts of the body (metastatic), with an abnormal phosphatidylinositol-3-kinase catalytic subunit alpha (PIK3CA) gene, and whose disease has progressed on or after endocrine therapy. Your health care provider will test your cancer for an abnormal “PIK3CA” gene to make sure that PIQRAY is right for you. It is not known if PIQRAY is safe and effective in children.

Patients should not take PIQRAY if they have had a severe allergic reaction to PIQRAY or are allergic to any of the ingredients in PIQRAY.

PIQRAY may cause serious side effects. PIQRAY can cause severe allergic reactions. Patients should tell their health care provider or get medical help right away if they have trouble breathing, flushing, rash, fever, or fast heart rate during treatment with PIQRAY. PIQRAY can cause severe skin reactions. Patients should tell their health care provider or get medical help right away if they get severe rash or rash that keeps getting worse, reddened skin, flu-like symptoms, blistering of the lips, eyes or mouth, blisters on the skin or skin peeling, with or without fever. PIQRAY can cause high blood sugar levels (hyperglycemia). Hyperglycemia is common with PIQRAY and can be severe. Health care providers will monitor patients’ blood sugar levels before they start and during treatment with PIQRAY. Health care providers may monitor patients’ blood sugar levels more often if they have a history of Type 2 diabetes. Patients should tell their health care provider right away if they develop symptoms of hyperglycemia, including excessive thirst, dry mouth, urinate more often than usual or have a higher amount of urine than normal, or increased appetite with weight loss. PIQRAY can cause lung problems (pneumonitis). Patients should tell their health care provider right away if they develop new or worsening symptoms of lung problems, including shortness of breath or trouble breathing, cough, or chest pain. Diarrhea is common with PIQRAY and can be severe. Severe diarrhea can lead to the loss of too much body water (dehydration) and kidney problems. Patients who develop diarrhea during treatment with PIQRAY should tell their health care provider right away.

Before taking PIQRAY, patients should tell their health care provider if they have a history of diabetes, skin rash, redness of skin, blistering of the lips, eyes or mouth, or skin peeling, are pregnant, or plan to become

pregnant as PIQRAY can harm their unborn baby. Females who are able to become pregnant should use effective birth control during treatment with PIQRAY and for 1 week after the last dose. Do not breastfeed during treatment with PIQRAY and for 1 week after the last dose. Males with female partners who are able to become pregnant should use condoms and effective birth control during treatment with PIQRAY and for 1 week after the last dose. Patients should also read the Full Prescribing Information of fulvestrant for important pregnancy, contraception, infertility, and lactation information.

Patients should tell their health care provider all of the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PIQRAY and other medicines may affect each other causing side effects. Know the medicines you take. Keep a list of them to show your health care provider or pharmacist when you get a new medicine.

The most common side effects of PIQRAY when used with fulvestrant are rash, nausea, tiredness and weakness, decreased appetite, mouth sores, vomiting, weight loss, hair loss, and changes in certain blood tests.

Please see full Prescribing Information for Piqray (PDF 1.0 MB)

Main image: Novartis scientists Francesco Hofmann, Christine Fritsch and Cornelia Quadt worked together to advance breast cancer therapy. Photo credit: Laurids Jensen

Lessons learned over decades power drug developers to find breast cancer therapy.

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