

How Combining Drugs May Be More Effective at Treating HER2-Positive Breast Cancer

Elena Shagisultanova, MD, PhD, is working to uncover effective treatments for HER2-positive breast cancer patients by combining different drugs to counteract the cancer cells' proliferation.

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When oncologist [Elena Shagisultanova](#), MD, PhD, joined the [University of Colorado Anschutz Medical Campus](#) in 2015, she started working in a clinic to help young women with breast cancer. She soon noticed that certain types of breast cancer — called HER2-positive and HR-positive — were more common than expected.

"I felt right away that the breast cancer that has both hormone receptors and HER2 was disproportionately prevalent among this population," said Shagisultanova, an associate professor of [medical oncology](#) in the [CU Department of Medicine](#), during a recent [Grand Rounds](#) presentation.

Shagisultanova has spent years researching HER2-positive breast cancer and treatment methods, including research supported by Pfizer through a more than \$1 million grant. It is work she continues today, aiming to uncover ways to more effectively treat this cancer.

"Currently, we have about four million women living with breast cancer in the United States," she said. "We, in medical oncology, work really hard to screen, prevent, treat, and cure breast cancer at the earliest stages, as well as help our patients live longer, better lives."

What is HER2?

HER2-positive breast cancer is a subtype of breast cancer in which breast tumor cells test positive for a protein called human epidermal growth factor receptor 2 (HER2). This protein helps cancer cells multiply.

"The effect of HER2 on cell signaling and proliferation of the cancer cells is very interesting, so I've spent my time working on HER2-positive breast cancer and trying to make a difference for these patients," she said.

Ultimately, the HER2 protein needs to be blocked to prevent this type of cancer from growing.

“If we don’t block HER2, we basically will not go anywhere in our treatment because the cancer cells will divide faster than we can kill them with chemotherapy,” she said.

Learning to block HER2

Research has found that HER2 can be blocked by certain drugs that act as HER2 inhibitors. For example, trastuzumab is a type of cancer drug that Shagisultanova said has “made a huge difference in the outcomes of patients.” Some other drugs that are used to treat this cancer include pertuzumab, margetuximab, ado-trastuzumab (T-DM1), ehnertu (T-DXd), and tucatinib.

“We have so many therapeutic agents — so why have we not cured this type of breast cancer yet?” she said. “Unfortunately, HER2-positive tumors can adapt and escape the effects of these targeted drugs.”

There are various receptors in the body that can be activated to rescue HER2-positive cancer cells, such as growth factor receptors, estrogen receptors, and other pathways that can help HER2-positive cells survive HER2 blockade, thus leading to the cancer’s growth. For example, if a patient takes a medicine like tucatinib to block HER2, this can lead to an increased expression of estrogen receptors in the tumor cells and the recruitment of estrogen “co-activators,” which provides a way for the cancer cells to survive.

“There is a crosstalk between estrogen receptors and HER2, which interferes a lot with our ability to successfully treat this cancer,” she said.

Research shows promise for triple-block approach

To overcome HER2’s ability to survive treatment with HER2-inhibitors, Shagisultanova and fellow researchers have been testing a “triple-block” approach. This means patients are prescribed three different types of targeted drugs to block HER2, estrogen receptors, and the CDK4/6 proteins controlling cancer growth with hopes that by combining these different drugs, the cancer will not be able to adapt and will be inhibited.

Shagisultanova’s lab team has found that if the triple-block approach is applied, every drug-resistant mechanism — meaning the previous ways that HER2-positive cancer cells avoided the medicine’s impact — is addressed, indicating the potential effectiveness of this approach.

“Essentially, we’ve proven that the triple-combination will work on multiple drug-resistant mechanisms, at least in my lab,” she said.

In 2016, Pfizer announced that Shagisultanova and [Virginia Borges](#), MD, deputy head of the Division of Medical Oncology, would receive support from its [Advancing Science Through Pfizer](#)

[Investigator Research Exchange](#) (ASPIRE) program. The goal of this research was to evaluate the safety and efficiency of this triple-block approach in patients with HER2-positive and HR-positive breast cancer.

The investigators found that, overall, the application of three targeted drugs — tucatinib, palbociclib, and letrozole — to treat HER2-positive breast cancer performed as well as a different chemotherapy-based drug combination that the Food and Drug Administration has approved.

“Of course, we’re not alone at CU in studying this. There is emerging data and other ongoing trials across the country,” she said.

Shagisultanova is now working in a cooperative group of researchers to design a study that looks at the triple-block of HER2, estrogen receptors, and CDK proteins for patients with early-stage breast cancer. These three drugs will be given to untreated cancer patients prior to them getting surgery, with the goal of shrinking their tumors.

“I hope we can make a big difference, especially in early-stage breast cancer,” she said.

When Shagisultanova worked on her first clinical trial, she realized there was an additional pathway that could help HER2-positive tumor cells adapt to targeted drug therapy and survive. This pathway, called the “PI3K/AKT pathway,” can be activated by drugs that aim to block HER2, and it can provide a way to rescue the cancer cells.

Research conducted by Shagisultanova has found that inhibiting this pathway’s signaling is an effective method of treating HER2-positive cancer. She is continuing to conduct research on potential drug combinations that are effective in inhibiting the HER2 and PIK3K/AKT pathways.

“Recently, several less toxic drugs that are PI3K/AKT pathway inhibitors have hit the market, and there are a few other drugs in development that are already showing promise. I think we will explore those in subsequent research,” she said.

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