Q&A: Behind the approvals—decades of research lead to a new generation of targeted cancer therapies

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Last month, the U.S. Food and Drug Administration (FDA) approved the use of the drug capivasertib, in combination with a current cancer

treatment called fulvestrant for patients with the most common type of breast cancer, the HR-positive/HER2-negative subtype. Known as an AKT inhibitor, the new drug works by targeting the AKT kinase, which is responsible for the growth and proliferation of certain tumors. The drug has been approved for use in breast cancer patients whose tumor has returned or become worse after treatment with chemotherapy or hormone-based therapies.

BIDMC's Alex Toker, Ph.D., a professor in the Department of Pathology, has focused on the AKT signaling pathway, and specifically on the AKT enzyme, for much of his scientific career. We asked him about how his body of work contributed to the recent FDA approvals and how decades of work coming to fruition will change the landscape for patients and their physicians in the years to come.

When did you first begin to study the enzyme targeted by the drug approved last month?

I've been working on this pathway and particularly on this one enzyme or protein kinase called AKT since I was a postdoc in the early 1990s. It was discovered in 1987, to be precise. So, it's taken 30-plus years to get a drug that's been FDA approved. It has been a long road. I and many other colleagues have been working on this enzyme and this pathway. Our cumulative evidence pointed to it being a great candidate for a drug for therapeutic benefit.

The drug itself targets the AKT enzyme's pathway. This pathway is hyperactive in many, many cancers, not just breast cancer; ovarian cancer, prostate cancer, brain, glioblastoma, endometrial. The drug has been in development for well over a decade, 15 years—that's a rough estimate—and there were many failures. Many of the initial drugs failed due to toxicities or lack of efficacy, not an uncommon experience in

oncology. As we learn more about the biology and the disease, the drugs have improved, both in terms of potency and efficacy.

Are there other drugs on the market today to which you significantly contributed?

We—and many other labs—have worked on and contributed to studies that in aggregate have contributed to approval to other drugs. For example, there's a protein that has been targeted in this pathway, an enzyme called PI3 kinase, and the first-in-class PI3 kinase inhibitor was approved in 2017.

PI3 kinase was discovered in the mid 1980s and, again, it's taken over 30, almost 40 years of research discovery, drug development, preclinical trials, clinical trials and ultimately FDA approval, for that drug to be approved. We are now four or five years on, and a lot more work has been done. There's a whole new class of drugs targeting PI3 kinase that are better, more potent and have fewer toxicities that are likely going to be approved in the coming years. We're going to see a dramatic increase in the number of options available to oncologists for treating patients with mutations in this pathway. There's a lot of excitement.

To what do you attribute this recent boom in treatment breakthroughs?

It's a cycle. It tends to be the cycle. If you look at the most frequently mutated oncogene in all cancers, it's called the RAS protein. PI3 kinases are the second most common. If you go back to the 1970s when people started targeting RAS, those drugs failed. It was only in the last five years that we finally have drugs that target RAS. That took even longer than AKT, somewhere between 30 and 40 years. For PI3 kinases, they are not far behind.

Drug development has taken this long because in many ways, it has taken this long to understand the biology, to generate sophisticated mouse models for the preclinical experiments that are required to initiate clinical trials. Now we have very sophisticated discovery and translational science in the laboratory. We have very sophisticated mouse models with which we can test these drugs, so our ability to discover drugs has improved dramatically. That's why the drug development pipeline has just exploded in the last decade and a half.

How or why did this approval come about now?

The drugmaker (AstraZeneca) was developing their compound, a combination of this drug in combination with standard of care endocrine therapies. They saw activity in preclinical models and in phase I and phase II clinical trials, leading up to a phase three clinical trial, which was first reported about a year ago and published in the *New England Journal of Medicine* this year (2023).

The phase III trial showed more than a doubling of what's called progression-free survival. When you see that, you know that the FDA is going to look at that very seriously and most likely approve it. This is a tremendous accomplishment because it is what's called first in class; that is to say, it is the very first drug to be approved to target a particular protein in any indication, any cancer, any lineage. It's something we've been waiting for since the early 1990s.

However, that is not to say it's the first line of treatment. It's approved for patients whose tumors have returned or become worse after two rounds of treatment. But this is likely to change over the next few years as this drug is now given, not in a clinical trial setting, but in what we call the real-world setting in clinics and hospitals in oncology wards all around the world.

As many more patients are treated and we see what the response rates are like and what it does in the real world, it's probably going to be moved up to second-line therapy. There are also many other phase II and III trials evaluating this drug and other AKT inhibitors in other combinations. So again, this has generated a lot of excitement in the oncology arena.

Provided by Beth Israel Deaconess Medical Center

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