Approval of First ‘Epigenetic’ Drug for a Solid Tumor Is Milestone

The approval will not only benefit current patients, but will also spur more research into the biology of other rare tumors.

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The approval of the drug tazemetostat to treat epithelioid sarcomas is a victory for patients and a vindication of the idea that success may take different forms in different cancers.

It’s also an affirmation of the value of research at Dana-Farber that began in the early 2000s with basic science discoveries and progressed into clinical trials that ultimately convinced U.S. Food and Drug Administration (FDA) officials of the drug’s merit.

Tazemetostat represents a new type of therapy for a disease often characterized as “ultra-rare” and “relentless.”

The first drug approval of its kind

Epithelioid sarcoma — a soft tissue cancer that occurs mainly in young adults and can quickly become metastatic — is usually treated with chemotherapy, which works for only a few months. Tazemetostat targets an enzyme within the cancer cells that is overly active because a gene that usually controls it is gone.

This type of indirect targeting is unusual: Most targeted drugs inhibit enzymes that are overactive because of a mutated gene or because the cell contains too many copies of the gene. Tazemetostat is an “epigenetic” drug because it alters the way these enzymes read the DNA instructions for cell division.

The FDA’s approval of tazemetostat, specifically for patients with advanced or metastatic epithelioid sarcoma who are not eligible for curative surgery, is the first approval of an epigenetic drug for a solid tumor. (Other epigenetic agents have been approved for blood cancers such as leukemia or multiple myeloma.)

A 20-year research journey

Dana-Farber has long been home to research in an aspect of epigenetics known as histone methylation, in which bundles of atoms called methyl groups (which serve as “epigenetic

markers") are attached to or removed from histones — proteins that act as spools for DNA storage. The placement of these markers can turn a gene's activity up or down.

Just over 20 years ago, Dana-Farber scientists began studying malignant rhabdoid sarcoma — an aggressive soft-tissue cancer in children — in which a portion of molecular machinery called "SWI/SNF remodeling complex" was missing, changing the way the DNA was read by the cell.

The missing protein within SWI/SNF is named SMARCB1. When the gene for SMARCB1 is deleted — or not "expressed" — the protein doesn't get made and the abnormal complex changes the way the cell is controlled. Researchers later found that SMARCB1 is lost in epithelioid sarcoma cells as well as rhabdoid sarcomas.

In the early 2000s, research led by Charles Roberts, MD, PhD, now the director of the Comprehensive Cancer Center at St. Jude's Children's Research Hospital, then a fellow in the laboratory of Stuart H. Orkin, MD, chair emeritus of Dana-Farber's Department of Pediatric Oncology and researcher at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, developed a mouse model that closely mirrors the sarcomas in humans.

Using the model, Roberts, Orkin, and their colleagues discovered that in sarcoma cells where the SWI/SNF complex lacks SMARCB1, the cells become dependent on another complex, called the polycomb repressor complex 2 (PRC2), for their growth. The business end of PRC2 is an enzyme called EZH2, which adds methyl groups to histones.

Putting the discovery into practice

Researchers quickly began to consider what the discovery could mean for the treatment of epithelioid and rhabdoid sarcomas. A drug capable of blocking EZH2 could, in theory, overcome the growth-stimulating effect of the loss of SMARCB1 and put the brakes on the cancer.

Between 2007 and 2014, Orkin and George Demetri, MD, senior vice president for Experimental Therapeutics and director of the Sarcoma Center at Dana-Farber collaborated with researchers at the newly created biotechnology company Epizyme™ in Cambridge's Kendall Square to develop the company's EZH2-inhibiting drug (originally known as EPZ-6438, now called tazemetostat).

In 2015, Dana-Farber investigators led by Demetri joined an international study of the drug in a small group of patients, and although the responses weren't as dramatic as researchers had hoped, they were intriguing enough to warrant further study. From 2015 to 2017, investigators at Dana-Farber, Massachusetts General Hospital (MGH), Memorial Sloan Kettering Cancer Center (MSKCC), as well as the National Cancer Institute of Italy, and several other center collaborated on a clinical trial of tazemetostat in patients with advanced epithelioid sarcomas, rhabdoid sarcomas, and other cancers that lacked SMARCB1 expression.

Of the 62 participants with epithelioid sarcoma, about 10% had their sarcoma shrink after taking the pill. For more than 60% of the participants, the cancer stopped worsening, even if their tumors

did not shrink. What particularly stood out about the results was the duration of the benefit: many patients had a benefit that lasted a year or more.

When Epizyme officials and clinical investigators initially presented these results to FDA regulators, there was skepticism about approving the drug for this group of patients.

“The panel members’ view was that although epithelioid sarcoma is a horrible disease, the agency doesn’t have a history of approving drugs based on trials involving only 60 patients and that show only a 10-12% response rate,” Demetri remarks.

Demetri and his colleagues in the U.S. and overseas, as well as at Epizyme, felt the FDA needed to take account of the extreme rarity of the disease (only about 150 patients a year are diagnosed with the disease in the U.S., and only 50 would be eligible for tazemetostat treatment per year). They explained that in a disease with such a bleak outlook for patients, a 10-12% response rate constitutes real progress, especially when so many of the responses are relatively durable. To discuss this in a public forum, the FDA organized a meeting of its Oncologic Drugs Advisory Committee (ODAC) at which Demetri and his associates made their case.

The result: an 11-0 vote by the ODAC on Dec. 18, 2019 in favor of approval of tazemetostat for adults with metastatic or locally advanced epithelioid sarcoma who aren’t eligible for curative surgery — leading to the FDA’s formal, accelerated approval on Jan. 23, 2020.

‘Small but significant’

The approval will not only benefit current patients, but will also spur more research into the biology of rare tumors lacking SMARCB1, including sarcomas, and the development of epigenetic drugs for other solid tumors, Demetri remarks.

“It’s especially rewarding when we can identify a cancer based not only on its appearance or where it originates but can uncover the biological mechanism that makes it different from other cancers,” he adds.

He applauds the FDA’s willingness to take a close look at tazemetostat and take into consideration the rarity and severity of the disease, noting the small but significant advance that the drug represents.

The approval also marks a key milestone in Dana-Farber’s decades-long involvement in epigenetic research and its role in the development and clinical testing of tazemetostat, Orkin says.

“It’s very gratifying when work in basic research leads to a hypothesis about a potential therapy and a prediction of how that therapy can be useful clinically,” he notes.

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