

CANCER RESEARCH

Melanoma Drug Vindicates Targeted Approach

A mutation-targeted molecular therapy has shown promise against one of the most devastating types of cancer, but how it works is unclear

Metastatic melanoma is one of the worst cancers. Average survival time at diagnosis is about 9 months, and many oncologists take a nihilistic attitude toward treatment. “They see patients with metastatic disease, and they say, ‘Well, you might as well make out your will; there’s really nothing for you,’” says Jeffrey Weber of the Moffitt Cancer Center in Tampa, Florida. The U.S. Food and Drug Administration approved the only metastatic melanoma drug, dacarbazine, in 1975. That drug has a 15% response rate, and all efforts to improve on that rate have failed.

Until this fall, “the skepticism that we would ever be able to break the back of this problem was particularly high,” says William Kaelin, a cancer researcher at the Dana-Farber Cancer Institute in Boston. So the 70% response rate reported in September in a phase I trial for a drug from the Berkeley, California, biotech company Plexxikon shocked the field. “It’s an astounding leap,” says trial principal investigator Keith Flaherty of Massachusetts General Hospital in Boston. “Way out of the ballpark of what ... we’ve ever seen with melanoma therapies in the past.” Patient numbers, though, are small, and the compound is not a magic bullet: Patients relapse, on average, after about 9 months, and a survival benefit has yet to be proven. But the Plexxikon compound, PLX4032, is changing the psychological landscape in the melanoma field. Researchers are scrambling to understand why it works in order to design new treatments for other cancers.

PLX4032 is a targeted molecular therapy, one of many now in development. It binds to and inactivates the BRAF protein, which is mutated in about 60% of melanomas. (A single mutation accounts for most of these.) Mutant BRAF turns on signaling in a pathway in cells that controls proliferation, and the drug’s efficacy validates the theory that targeting this pathway would destroy tumors. Skepticism had been widespread. “There were many who thought, ‘Well, BRAF mutations, who cares?’” says Flaherty. “‘These tumors have so many mutations that there’s no one oncogene that’s going to be so important.’”

Melanoma trials of other compounds targeting BRAF and a downstream protein, MEK, did not succeed. K. Peter Hirth, the

CEO of Plexxikon, says that PLX4032 works because it’s “clean”: It binds to the mutant form of BRAF much better than it does normal, “wild-type” BRAF. “You really need to have more than 90% pathway inhibition” of BRAF signaling to shut it down, he says. Because it binds preferentially to a target that exists only in tumors, the drug can be given in high doses to patients before serious side effects appear.

PLX4032 is “unlike any targeted therapy anytime in the past,” says David Solit, a researcher at the Memorial Sloan-Kettering

activate the pathway in nonmutant cells. Three other research groups have recently reported similar activating activity for RAF inhibitors in normal cells.

That pathway activation in normal cells could explain why side effects don’t show up at high doses, speculates Frank McCormick, a cancer researcher at the University of California, San Francisco: “You don’t have to worry about side effects of shutting down the pathway.”

Pathway activation in normal cells may help, but it could also account for a worrisome side effect. Some PLX4032 patients develop skin lesions known as keratoacanthomas. Researchers suspect the drug might be activating the pathway in skin cells predisposed to growth, hence the tiny lesions. They’re benign, but they hint that long-term drug treatment could convert precancerous growths into non-melanoma cancer.

Regardless of how it works, PLX4032 validates the theory that targeting early “driver” mutations is a feasible way to treat common cancers. “The hope was that by understanding the molecular biology, and in particular identifying the driver mutations, we would make progress,” says Kaelin. “This is a very significant step forward.”

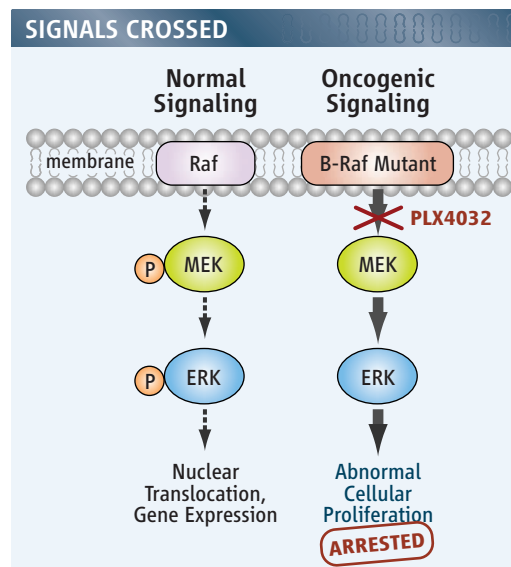
BRAF mutations are also found in about 10% of colorectal cancers, and less frequently in lung and other cancers—in about 7% of all tumors overall. In theory, PLX4032 should work in all of them. A clinical trial in colorectal cancer is nearly complete.

Whether other cancer mutations can be practically targeted remains to be seen. Cancer genome sequencing efforts suggest that mutations are high in number and low in frequency (*Science*, 5 September 2008, p. 1280).

Many drugs might prove necessary for any single tumor type, one for each driver mutation. Kaelin anticipates “drips and drabs of different mutations” in different cancers. “But I’m hoping there are at least a few more of these ... highly prevalent mutations waiting to be discovered.” And drug resistance is inevitable, as PLX4032 confirms. “It’s going to have to be ... combinations of two or three drugs that can really effectively kill the tumors,” says McCormick. Still, the melanoma results allow researchers to go forward with some confidence. Says Kaelin, “This is a hopeful piece of data that we’re on the right track.”

—KEN GARBER

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Roadblock. Plexxikon’s drug interrupts a key signaling pathway in tumor cells, but not normal cells.

Cancer Center in New York City. “It seems to be inhibitory of the pathway ... only in tumors with the mutation. And that could lead to a change in the way we try to design drugs.”

But how the drug works remains unclear. “Why is it so selective for just the mutant?” asks Solit. One possibility is that the drug at high doses binds to wild-type BRAF or other RAF family members in a way that allows the signaling pathway to be active in normal cells instead of shutting it down. For example, a group from the biotech company Genentech presented data at the Molecular Targets and Cancer Therapeutics meeting in November in Boston showing that the same RAF inhibitors that block the pathway in BRAF mutant cells