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Studies show new drug to be effective in treating skin cancer

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A new drug has been shown to be effective in treating and preventing the most common cancer in the United States: basal cell carcinoma skin cancer, according to a new study in the *New England Journal of Medicine* to be published June 7.

The drug, vismodegib (trade name: Erivedge), was tested in a clinical trial in patients with Gorlin syndrome, a rare disease in which individuals have tens to hundreds of disfiguring basal cell carcinoma tumors. The findings are being released in conjunction with two other papers in the same journal issue that show the effectiveness of vismodegib in treating BCCs that are advanced or metastatic. All three articles include authors from the Stanford University School of Medicine.

"It is a landmark day for patients with basal cell carcinoma and all those involved in their care — the greatest advance in therapy yet seen for this disease," writes John Lear, MD, in an accompanying editorial. Lear is a consultant dermatologist at Manchester Royal Infirmary and the Dermatology Centre of Hope Hospital in Manchester, UK.

The research is being published five months after vismodegib became the first drug in its class to gain approval from the U.S. Food and Drug Administration. Vismodegib, which was developed by the biotech firm Genentech/Roche, targets a molecular signaling pathway in cells called the Hedgehog signaling pathway. The drug works by inhibiting the Hedgehog pathway, which is inappropriately activated in basal cell carcinomas. While the pathway is important in early embryonic

development, it is generally inactive in healthy adults. In January, the FDA approved the drug for use in treating advanced forms of basal cell carcinoma.

In the study of the drug's effect on patients with Gorlin syndrome (also known as Basal Cell Nevus Syndrome) the researchers showed that subjects taking vismodegib developed an average of two new tumors per year, compared with 29 new tumors in subjects taking placebo. The drug is taken daily in a pill form. This investigator-initiated, double-blind placebo trial involved 41 patients with Gorlin syndrome and was stopped early due to the overwhelming effectiveness of vismodegib, the article states. It was considered unethical not to offer the drug to those participants taking a placebo.

"How often in your life do you get to have worked within a field where you finally get to test to a drug that actually changes people's lives?" said Jean Tang, MD, PhD, assistant professor of dermatology at Stanford and first author of the study. "We were very excited about the results."

She added: "In most subjects, all the carcinomas clinically disappeared. No tumors progressed while the subjects took vismodegib."

Currently there is no good treatment for Gorlin syndrome, which afflicts one in 50,000 people; these individuals often develop their first BCC tumor in childhood. The constant growth of BCC tumors, while generally non-lethal, can be treated surgically but the persistent operations leave scarring, and some BCC tumors can eventually become inoperable.

"These patients usually have severe scarring by the time they reach adulthood," Tang said. "The cancer generally doesn't kill you, but obviously it affects the quality of life. Many patients never marry, never have families, they face more limited job opportunities. There currently

are no good treatment options."

The drug did not permanently cure patients of their tumors, as the BCC tumors returned once the treatment was stopped, although very slowly. Side effects include mild taste loss, muscle cramps, mild hair loss and weight loss, and discontinuation rates by patients were high. Tang previously worked as a postdoctoral scholar with the senior author of the study Ervin Epstein, MD, at Children's Hospital of Oakland Research Institute.

About 2.8 million U.S. patients are diagnosed each year with basal cell carcinoma, which is generally caused by sun exposure and cured by surgical removal or radiation treatment. But in rare cases, known as locally advanced disease, the tumorous lesions invade nearby tissues and can become disfiguring or even metastasize and spread elsewhere in the body. It is rarely fatal, but can be painful and lead to other complications.

The second of the three papers presents the findings from the phase-2 Genentech-sponsored clinical trial that were the basis for the FDA's decision to allow vismodegib to be used to treat advanced forms of BCC in adults. The drug was successful 43 percent of the time in either complete or partial shrinkage of tumors in the 96 patients with advanced disease who participated in the trial, the study reports.

In the third article — a letter to the editor detailing a case study of a 41-year-old man who had skin cancers all over his body caused by a unique genetic mutation in the Hedgehog pathway different from Gorlin syndrome — the cancer still responded well to vismodegib. This suggests that Hedgehog-inhibiting drugs like vismodegib could be successful in treating a variety of other invasive cancers caused by abnormalities in the pathway, said Anthony Oro, MD, PhD, senior author of the letter and a professor of dermatology at Stanford.

The publication of the papers is a milestone in what has been a global effort to develop a new cancer treatment that can be traced back about 16 years. That's when biologists, including a group led by Epstein and Stanford professor of developmental biology Matthew Scott, PhD, first linked the Hedgehog pathway to human cancer. Since that initial discovery, scientists have been intensely studying the pathway searching for drugs that can treat cancers by blocking it. Now that one drug has been found, there are five or six other companies developing similar drugs, each of which may benefit patients, Oro said.

"We now have a brand new class of drugs that can treat these cancers," Oro said. "As a dermatologist, this is exciting to see. There is nothing for these patients that works. Their cancers are often surgically inoperable."

The drug also comes with a boxed warning of the potential risks of death and of severe birth defects to unborn babies. It costs $7,500 per month. The duration of treatment per patient is expected be around 10 months.

More information: "Inhibiting the Hedgehog Pathway in Basal Cell Nevus Syndrome Patients" *New England Journal of Medicine*, 2012.

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