New Drug for Blood Cancers Now in Five Phase II Clinical Trials

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Researchers at University of California, San Diego School of Medicine have established the safety and dosing of a new drug for treating blood cancers. The findings are published online July 27 in *The Lancet Haematology*.

The drug is a small molecule inhibitor that suppresses the activity of a signaling pathway believed to contribute to a variety of blood cancers' eventual resistance to standard chemotherapy treatments.

More specifically, preclinical research, funded in part by the California Institute for Regenerative Medicine (CIRM), has shown that the drug coaxes dormant cancer stem cells, residing in the bone marrow, to begin differentiating and exit into the blood stream where they can be destroyed by chemotherapy agents targeting dividing cells.

"This drug gets that unwanted house guests to leave and never come back," said the study's senior author Catriona Jamieson, MD, PhD, an associate professor of medicine and chief of the Division of Regenerative Medicine in the School of Medicine. "It's a significant step forward in treating people with refractory or resistant myeloid leukemia, myelodysplastic syndrome and myelofibrosis. It's a bonus that the drug can be administered as easily as an aspirin, in a single, daily oral tablet."

The drug's name is PF-04449913, Pfizer's alphanumeric designation for an investigational medication. PF-04449913 targets the sonic Hedgehog signaling pathway, one of the key regulators of vertebrate embryonic development and the regeneration of adult tissues.

For the first-in-human study, funded in large part by Pfizer, 47 adults with blood and marrow cancer received escalating daily doses of the drug in 28-day cycles. Treatment cycles were repeated until a participant experienced unacceptable adverse effects without evidence of clinical improvement. Those who showed clinical activity from the drug, without serious side-effects, received additional treatment cycles. The phase 1 clinical trial was conducted at three medical centers in the United States, including UC San Diego Health, and one center in Italy from 2010 to 2012.

Of the 47 study participants, 28 individuals, or 60 percent of the group, experienced treatment-related problems. Adverse effects were severe, however, in only three people. The drug elicited clinical activity sufficient to establish proof-of-concept for the treatment in 23 individuals, or nearly half the study participants.

Given the promising results, the drug's efficacy as a treatment for different types of blood cancer is now being investigated in five phase II clinical trials, three of which are currently recruiting participants at UC San Diego Health.

"Our hope is that this drug will enable more effective treatment to begin earlier and that with earlier intervention, we can alter the course of disease and remove the need for, or improve the chances of success with, bone marrow transplantation," Jamieson said. "It's all about reducing the burden of disease by intervening early."

"This new drug highlights the value of understanding stem cell signaling pathways as a tool for developing truly novel approaches for improving human health," said C. Randal Mills, PhD, president and CEO of CIRM, California's stem cell agency.

Co-authors include Giovanni Martinelli, Cristina Papayannidis, and Michele Baccarani, University of Bologna, Italy; Vivian G Oehler, and Jerald Radich, Fred Hutchinson Cancer Research Center, Seattle; Rachel Courtney, M Naveed Shaik, Karen R McLachlan, Xianxian Zheng, and Wendy J Levin, Pfizer Oncology, La Jolla; Xiaoxi Zhang, Pfizer Oncology, New York; Ashleigh O'Connell, Pfizer Oncology, Collegeville; and Hagop M Kantarjian, and Jorge E Cortes, MD Anderson Cancer Center, Houston.

In addition to funding from CIRM and Pfizer, the European Leukemia Net also provided support for the study.

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