Nature Immunology Paper Highlights Potential Role of FAK Inhibition in Hematological Malignancies

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Research from UC Irvine, Massachusetts General Hospital and Tufts Medical Center Points to Potential Development of Verastem FAK inhibitors in subset of Acute Lymphoblastic Leukemia

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 10, 2014-- Verastem, Inc. (NASDAQ:VSTM), focused on discovering and developing drugs to treat cancer by the targeted killing of cancer stem cells, today announced that a publication in Nature Immunology demonstrates the scientific rationale for FAK inhibition in B cell-ALL.

“Loss-of-function in the transcription factor Ikaros appears to create a differentiation block that drives the pre-B cells into an adhesive state, promotes self-renewal and primes them for malignant potential,” said Richard Van Etten, M.D., Ph.D., Professor of Medicine, UC Irvine and Director, Chao Family Comprehensive Cancer Center. “In the current study, we demonstrate that treatment with the Verastem FAK inhibitor VS-6062 targets these malignant B-cells and leads to apoptotic cell death.”

The Nature Immunology article can be accessed at: http://bit.ly/1bKYJ6M.

Human precursor B cell (pre-B cell) acute lymphoblastic leukemia (B-ALL) has an estimated incidence of 8,000 new cases per year in the US of which a substantial portion contain the mutant form of Ikaros.

“Historically, leukemia has been one of the diseases most closely linked to cancer stem cells,” said Jonathan Pachter, Ph.D., Verastem Head of Research. “High-risk B-ALL cancer has a loss-of-function in the Ikaros transcription factor. This study provides intriguing clues on a possible use of our FAK inhibitors in a specific subset of patients that lack Ikaros.”

Verastem is currently conducting multiple trials of two FAK inhibitors: VS-6063 (defactinib) and VS-4718. VS-6063 is in the registration-directed COMMAND study (www.COMMANDmeso.com) for patients with mesothelioma, a Phase 2 study in NSCLC, a Phase 1/1b combination study of VS-6063 and weekly paclitaxel for patients with ovarian cancer and a Phase 1 trial in Japanese patients. VS-4718 is in a Phase 1 study for patients with advanced cancers.

In separate papers published in the January 17th issue of Science, modulation of the Ikaros transcription factor was described as a potential mechanism of action for lenalidomide (Revlimid®) http://bit.ly/1inNx1D.

"At Verastem, we are focusing on moving rapidly through late stage studies in cancers with a defined patient population that are particularly sensitive to our drug candidates. The Nature Immunology and Science papers suggest that hematological malignancies could be an added area where we may be able to help patients in need," said Christoph Westphal, M.D., Ph.D., Verastem Executive Chairman.

The Nature Immunology article can be accessed at http://bit.ly/1bKYJ6M and the abstract is below:

Loss of Ikaros DNA-binding function confers integrin-dependent survival on pre-B cells and progression to acute lymphoblastic leukemia
Ila Joshi, Toshimi Yoshida, Nilamani Jena, Xiaoqing Qi, Jiangwen Zhang, Richard A Van Etten, & Katia Georgopoulos
Published online February 9, 2014. Nature Immunology (2014) doi:10.1038/ni.2821

Deletion of the DNA-binding domain of the transcription factor Ikaros generates dominant-negative isoforms that interfere with its activity and correlate with poor prognosis in human precursor B cell (pre-B cell) acute lymphoblastic leukemia (B-ALL). Here we found that conditional inactivation of the Ikaros DNA-binding domain in early pre-B cells arrested their differentiation at a stage at which integrin-dependent adhesion to niches augmented signaling via mitogen-activated protein kinases, proliferation and self-renewal and attenuated signaling via the pre-B cell antigen receptor and the differentiation of pre-B cells. Transplantation of polyclonal Ikaros-mutant pre-B cells resulted in long-latency oligoclonal pre-B-ALL, which demonstrates that loss of Ikaros contributes to multistep B cell leukemogenesis. Our results explain how normal pre-B cells transit from a highly proliferative and stroma-dependent phase to a stroma-independent phase during which differentiation is enabled, and suggest potential therapeutic strategies for Ikaros-mutant B-ALL.

The articles from the January 17, 2014 edition of Science can be accessed through the links below:

How thalidomide works against cancer
A. Keith Stewart
Science. 2014 Jan 17;343(6168):256-7
Link: http://bit.ly/19OnNLf

Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells
Jan Krönke, Namrata D. Udeshi, Anupama Narla, Peter Grauman, Slater N. Hurst, Marie McConkey, Tanya Svinkina, Dirk Heckl, Eamon Comer, Xiaoyu Li, Christie Ciarlo, Emily Hartman, Nikhil Munshi, Monica Schenone, Stuart L. Schreiber, Steven A. Carr, and Benjamin L. Ebert
Science. 2014 Jan 17;343(6168):301-5
Link: http://bit.ly/1e23bdI

The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins
Gang Lu, Richard E. Middleton, Huahang Sun, MarkVic Naniong, Christopher J. Ott, Constantine S. Mitsiades, Kwok-Kin Wong, James E. Bradner, and William G. Kaelin Jr.

Science. 2014 Jan 17;343(6168):305-9
Link: http://bit.ly/1eomxji

About VS-6063

VS-6063 (defactinib) is an orally available compound designed to target cancer stem cells through the potent inhibition of focal adhesion kinase (FAK). Cancer stem cells are an underlying cause of tumor resistance to chemotherapy, recurrence and ultimate disease progression. Research by Robert Weinberg, Ph.D., scientific cofounder and chair of Verastem's Scientific Advisory Board, and Verastem has demonstrated that the FAK pathway is critical for the growth and survival of cancer stem cells. VS-6063 is currently being studied in the registration-directed COMMAND trial in mesothelioma (www.COMMANDmeso.com), a Phase 1/1b study in combination with paclitaxel for patients with ovarian cancer, a Phase 1 study in Japan in patients with advanced solid tumors and a Phase 2 trial in patients with Kras-mutated non-small cell lung cancer. VS-6063 has been granted orphan drug designation in the U.S. and E.U. for use in mesothelioma.

About VS-4718

VS-4718 is an orally available compound designed to target cancer stem cells through the potent inhibition of focal adhesion kinase (FAK). VS-4718 is currently being studied in a Phase 1 dose escalation study in patients with advanced cancers.

About Verastem, Inc.

Verastem, Inc. (NASDAQ:VSTM) is discovering and developing drugs to treat cancer by the targeted killing of cancer stem cells. Cancer stem cells are an underlying cause of tumor recurrence and metastasis. Verastem is developing small molecule inhibitors of signaling pathways that are critical to cancer stem cell survival and proliferation: FAK, PI3K/mTOR and Wnt. For more information, please visit www.verastem.com.

Forward-looking statements:

This press release includes forward-looking statements about the Company's strategy, future plans and prospects, including statements regarding the development of the Company's compounds, including VS-6063, or defactinib VS-4718, VS-6062 and the Company's FAK inhibition program, the timeline for clinical development and regulatory approval of the Company's compounds, the expected timing for the reporting of data from ongoing trials, and the structure of the Company's planned or pending clinical trials, and potential indications for clinical development. The words "anticipate," "appear," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include the risks that the preclinical testing of the Company's compounds and preliminary data from clinical trials may not be predictive of the results or success of ongoing or later clinical trials, that data may not be available when we expect it to be, that the Company will be unable to successfully complete the clinical development of its compounds, including VS-6063 and VS-4718, that the development of the Company's compounds will take longer or cost more than planned, and that the Company's compounds will not receive regulatory approval or become commercially successful products. Other risks and uncertainties include those identified under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2012 and in any subsequent SEC filings. The forward-looking statements contained in this presentation reflect the Company's current views with respect to future events, and the Company does not undertake and specifically disclaims any obligation to update any forward-looking statements.

Source: Verastem, Inc.

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