Verastem Presents Data at the 2014 American Society of Hematology Annual Meeting

December 8, 2014

BOSTON--(BUSINESS WIRE)--Dec. 8, 2014-- Verastem, Inc. (NASDAQ: VSTM), focused on discovering and developing drugs to treat cancer by the targeted killing of cancer stem cells, today announced oral and poster presentations at the 2014 American Society of Hematology (ASH) Annual Meeting and Exposition taking place December 6 - 9, 2014, in San Francisco.

“High risk B-ALL characterized by Ikaros mutation remains an unmet medical need with limited treatment options,” said Richard A. Van Etten, M.D., Ph.D., Director, Chao Family Comprehensive Cancer Center at the University of California Irvine. “The data presented at ASH identify an important role of FAK in this disease setting, and demonstrate compelling preclinical proof of concept with the FAK inhibitors VS-4718 and VS-6063. These data provide a rationale for clinical evaluation of FAK inhibitors in B-ALL.”

“Cancer stem cells are an underlying driver of many cancer types and our product candidates have now demonstrated activity in preclinical models of both solid and hematological malignancies,” said Jonathan Pachter, Ph.D., Verastem Head of Research. “One commonality evident from the presentations at ASH this year is that multiple hematopoietic malignancies rely on bone marrow stromal interactions in a FAK/PYK2-dependent manner. Cancer stem cells in both AML and B-ALL are highly dependent on stromal interactions to survive, and FAK/PYK2 inhibitors kill cancer stem cells by disrupting these stromal interactions. Collectively, this research supports advancing VS-4718 into patients with hematological malignancies through our planned Phase 1 study in early 2015.”

These data are being presented in support of the Company’s ongoing research and development programs. Two of Verastem’s product candidates, VS-6063 and VS-4718, target cancer stem cells through potent inhibition of focal adhesion kinase (FAK). The FAK family consists of the closely related kinases FAK and proline-rich tyrosine kinase 2 (PYK2). FAK and PYK2 are the only two members of the FAK family. The effect of PYK2 inhibition by VS-4718 was described in a recently published study in the journal *Blood* where the anti-cancer activities of VS-4718 in preclinical models of hematological malignancy were explored.

A summary of the data presented at ASH is below:

Oral Presentation

Title: Focal Adhesion Kinase Inhibitors Reverse the Stromal Adhesion Phenotype of Ikaros-Mutant B-ALL, Induce Apopotosis, and Synergize with ABL1 Tyrosine Kinase Inhibitors: A New Paradigm for Pathogenesis and Therapy of High-Risk B-ALL
Abstract #: 285
Session: 618. Acute Lymphoblastic Leukemia: Preclinical Models
Date and Time: Monday, December 8, 2014: 7:30 AM PT
Location: West Building, 3002-3004 (Moscone Center)
Summary: B-cell acute lymphoblastic leukemia (B-ALL) is a malignancy of precursor B-lymphocytes affecting both children and adults. Deletions and dominant-negative mutations in IKZF1, the gene encoding the Ikaros transcription factor, are found in ~85% of Philadelphia chromosome-positive (Ph+) B-ALL and in some cases of Philadelphia chromosome-negative (Ph-) B-ALL, and are associated with poor prognosis. Genomic studies of high-risk Ph- or “Ph-like” B-ALLs have revealed frequent mutation and activation of tyrosine kinase (TK) genes and signaling pathways. While ABL1 tyrosine kinase inhibitors (TKIs) such as dasatinib and imatinib have been added to chemotherapy regimens for Ph+ B-ALL, over half of these patients will still relapse, which correlates with residual disease burden in the bone marrow (BM) following induction therapy. Hence, new therapeutic strategies are needed for patients with Ikaros-mutant, high-risk Ph+ and Ph- B-ALL. Prior research has shown that Ikaros DNA-binding function is required in the B-lymphoid lineage for transition from the large to small pre-B cell stage of differentiation, and that arrest at this stage of development can give rise to B-ALL. The survival and proliferation of Ikaros mutant pre-B cells is dependent on increased integrin-mediated stromal adhesion and activation of FAK. The effects of FAK inhibitors, VS-4718 and VS-6063 (defactinib), on B-ALL were investigated in the current study.

The research results demonstrated that BCR-ABL1 cooperates with Ikzf1 mutation to accelerate B-leukemogenesis in mice. BCR-ABL1+ Ikaros-mutant B-ALLs exhibit stroma-mediated resistance to ABL1 TKIs, while the FAK inhibitors VS-4718 and VS-6063 were effective in blocking stromal adhesion and inducing apoptosis in both mouse and human Ikaros-mutant B-ALL samples. Collectively, these observations suggest a new model to explain the pathogenesis of high-risk B-ALL and its resistance to therapy. B-ALLs with IKZF1 mutations may be resistant to TKIs and to chemotherapy by virtue of their stromal adhesion phenotype, resulting in failure to eliminate BM leukemic stem cells. Inhibition of FAK signaling in Ph+ or Ph IKZF1-mutant B-ALL may reverse the stromal-mediated resistance to ABL1 TKIs and/or chemotherapy. These results support the further investigation of FAK inhibitors for the treatment of high-risk IKZF1-mutant B-ALL patients.

A copy of the oral presentation is available at http://bit.ly/R3M6wc

Poster Presentations

Title: VS-4718, a Potent Focal Adhesion Kinase (FAK) Inhibitor, Exhibits Anticancer Activity in Leukemia Models in Vitro and in Vivo
Abstract #: 982
Session: 616. Acute Myeloid Leukemia: Novel Therapy, excluding Transplantation: Poster I
Date and Time: Saturday, December 6, 2014, 5:30 PM-7:30 PM PT
Location: North Building, Hall E (Moscone Center)
Summary: Current chemotherapy for leukemia is effective in killing leukemic blasts in the periphery, but not leukemic stem cells (LSCs) in the bone marrow, which are thought to be responsible for the high relapse rate in leukemia. Thus, new therapies that effectively target LSCs are urgently needed to prevent cancer relapse. Accumulating evidence supports an essential role for adhesion pathways: particularly integrin beta 3 and its

downstream target FAK in the maintenance of LSCs. It has been previously shown that FAK inhibitors preferentially target cancer stem cells in solid tumors. VS-4718 is a potent, orally bioavailable small molecule that targets cancer stem cells through inhibition of FAK and PYK2. In this study, the effects of VS-4718 were investigated in hematological malignancies.

The anti-proliferative effect of VS-4718 was evaluated in a panel of 10 cell lines derived from patients with acute promyelocytic leukemia (APL), T-cell acute lymphocytic leukemia (T-ALL), B-cell acute lymphocytic leukemia (B-ALL), chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). VS-4718 displayed anti-proliferative effects against most of these cell lines, with MV4-11 AML being the most sensitive with an EC50 of 100 nM. The in vivo efficacy of VS-4718 in both subcutaneous and disseminated xenograft models of AML using the MV4-11 cell line was then further investigated. Nude mice bearing subcutaneous MV4-11 tumors were treated orally twice daily (BID) with either vehicle control or VS-4718 for 14 days. The 75 mg/kg dosage of VS-4718 caused 50% tumor growth delay and significantly extended median survival of mice from 28 days to 48 days ($p<0.05$). Moreover, tumor regression was observed in 4 out of 10 mice. Observations were then extended to a disseminated MV4-11 AML model to incorporate bone marrow stromal biology. When compared with vehicle control, VS-4718 dosed at 25 or 75 mg/kg, on an oral BID dosing schedule for 14 days, resulted in a 40% and 76% increase in mouse life span, and significantly extended survival ($p<0.05$ and $p<0.001$ [log rank test]), respectively. In summary, this research demonstrated that VS-4718 has anti-proliferative activity in certain subtypes of AML cell lines, those with EC50 values of 95 nM – 5μM, and in primary AML. In addition, inhibition of FAK/PYK2 activity by VS-4718 induced tumor regression and significantly increased survival in the in vivo models of AML. Taken together, these results suggest that VS-4718 displays anticancer activity in leukemia models both in vitro and in vivo. A Phase 1 safety and dose-finding study in patients with relapsed or refractory acute leukemias is planned.

A copy of the poster presentation is available at http://bit.ly/R3M6wc

Title: Proline-Rich Tyrosine Kinase (Pyk2) Promotes Tumor Progression in Multiple Myeloma (MM) and Represents a Novel Target for Therapy in MM
Abstract #: 2101
Session: 652. Myeloma: Pathophysiology and Pre-Clinical Studies, excluding Therapy: Poster I
Date and Time: Saturday, December 6, 2014, 5:30 PM-7:30 PM PT
Location: West Building, Level 1 (Moscone Center)
Summary: PYK2 is a non-receptor tyrosine kinase which belongs to the FAK family, however, its role in modulating multiple myeloma (MM) biology and disease progression remains unexplored. In this study, the tumor-promoting role of PYK2 in MM is described, thus providing molecular evidence for a novel tyrosine kinase inhibitor. Gene profiling (GEP) and Cancer Cell Line Encyclopedia (CCLE) analysis and immunohistochemstry were performed to evaluate PYK2 expression in MM. Gain- and loss-of function assays were performed on certain MM cells to confirm tumor-promoting role of PYK2 in MM. In vivo tumor growth, PYK2-dependent-modulation of β-catenin signaling activity, and inhibitory effects of VS-4718 on FAK and PYK2 activity were all evaluated.

The research results demonstrated that PYK2 is highly expressed in MM and PYK2 silencing decreased MM tumor growth and prolonged survival in a mouse xenograft model. In addition, overexpression of PYK2 promoted MM tumor progression in a mouse xenograft model. The study results also demonstrated VS-4718-dependent induction of apoptosis, suppression of cellular migration, and modulation of cell cycle in PYK2/high MM versus PYK2/low MM cells. VS-4718 also reduced survival of primary myeloma bone marrow derived CD138+ cells without affecting viability of peripheral blood-derived mononuclear cells. VS-4718 treatment effectively reduced MM tumor growth compared with vehicle control. VS-4718 also inhibited b-catenin expression. Taken together, these results demonstrated the tumor-promoting role of PYK2 in MM, describe the implication of PYK2 in facilitating the oncogenic Wnt/β-catenin pathway, and support the potential clinical development of a FAK/PYK2 inhibitor, such as VS-4718, for the treatment of MM.

A copy of the poster presentation is available at http://bit.ly/R3M6wc

Title: Targeting PYK2 Mediates Microenvironment-Specific Myeloma Cell Death
Abstract #: 2081
Session: 652. Myeloma: Pathophysiology and Pre-Clinical Studies, excluding Therapy: Poster I
Date and Time: Saturday, December 6, 2014, 5:30 PM-7:30 PM PT
Location: West Building, Level 1 (Moscone Center)
Summary: MM remains an incurable malignancy due, in part, to the influence of the bone marrow microenvironment on survival and drug response. Identification of microenvironment-specific survival signaling determinants is critical for the rational design of therapy and elimination of MM. Prior research has shown that collaborative signaling between β1 integrin-mediated adhesion to fibronectin (FN) and Interleukin-6 (IL-6) results in increased STAT3 phosphorylation and a more malignant phenotype. In the current study, it was hypothesized that the collaborative signaling between β1 integrin and gp130 was mediated by focal adhesion (FA) formation and PYK2 kinase activity.

The research results demonstrated that PYK2 mediates the amplification of JAK1/STAT3 signaling in adherent myeloma cell lines and in CD138-enriched myeloma patient specimens. Both pharmacological and molecular targeting of PYK2 reduced the amplification of STAT3 phosphorylation. Further, co-culture of MM cells with patient BMSCs showed similar β1 integrin-specific enhancement of PYK2, JAK1, STAT3 signaling. Importantly, molecular and pharmacological targeting of PYK2 specifically induced apoptosis and reduced clonogenic growth in BMSC-adherent myeloma cell lines, ALDH+ MM cancer stem cells, and patient specimens. These data identify a novel PYK2-mediated survival pathway in MM cells and MM cancer stem cells activated within the context of microenvironmental cues, suggesting that PYK2 may be a therapeutic target. Moreover, these data provide preclinical support for the use of the clinical stage FAK/PYK2 inhibitors for treatment of MM, especially in a minimal residual disease (MRD) setting.

A copy of the poster presentation is available at http://bit.ly/R3M6wc

Title: PYK2 Inhibitors Sensitize Hypoxia-Induced Drug Resistant Multiple Myeloma Cell
Abstract #: 4704
Session: 652. Myeloma: Pathophysiology and Pre-Clinical Studies, excluding Therapy: Poster III
Date and Time: Monday, December 8, 2014, 6:00 PM-8:00 PM PT
Location: West Building, Level 1 (Moscone Center)
Summary: MM is a plasma cell malignancy, characterized by plasma cell accumulation in the bone marrow (BM) and hyperproduction of immunoglobulin G (IgG). Despite the implementation of novel therapies, more than 70% of MM patients relapse due to drug resistance and MRD attributed to cancer stem cells. The hypoxic nature of the BM plays a critical role in MM cells acquiring a stem cell-like phenotype, and together with cellular and acellular components of the BM microenvironment contributes to drug resistance leading to MRD. In this study, inhibition of PYK2, using the dual FAK/PYK2 inhibitors VS-4718 and VS-6063, was evaluated, along with investigation of the reversibility of the hypoxia-inducible stem cell-like

phenotype of MM cells and sensitizing them to therapy both *in vitro* and *in vivo*. MM cell lines (MM1s, RPMI8226 and H929) were treated with the FAK/PYK2 inhibitors VS-4718 or VS-6063 in the presence or absence of bortezomib under normoxic and hypoxic conditions. MM cells were then analyzed for cell proliferation/survival. The effect of VS-6063 and VS-4718 on sensitization of bortezomib-resistant MM cells were also tested in three *in vivo* models.

The research results demonstrated that FAK/PYK2 inhibitors, VS-4718 and VS-6063, decreased proliferation and increased apoptosis of MM cells as single agents. Hypoxia-induced resistance to proteasome inhibitors and the PYK2 inhibitors resensitized MM cells to therapy *in vitro* and *in vivo*. Moreover, FAK/PYK2 inhibitor VS-4718 was able to prevent relapse in an *in vivo* MM model simulating MRD. These data provide a basis for future clinical trials to sensitize relapsed/refractory MM patients to therapy by FAK/PYK2 inhibitors and their use to reduce relapse post front-line treatment in an MRD setting.

A copy of the poster presentation is available at http://bit.ly/R3M6wc

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 FAK activity 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 "Window of Opportunity" study in patients with mesothelioma prior to surgery, a Phase 1/1b study in combination with paclitaxel in patients with ovarian cancer, and a trial in patients with Kras-mutated non-small cell lung cancer. VS-6063 has been granted orphan drug designation in the U.S. and EU 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 and activity of the Company's product candidates, including VS-6063, or defactinib, and VS-4718, and the Company's FAK and PI3K/mTOR programs generally, the timeline for clinical development and regulatory approval of the Company's product candidates, including the planned commencement a Phase 1 study of VS-4718 in patients with hematological malignancies in early 2015, and the structure of the Company's planned or pending clinical trials. 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 product candidates and preliminary or interim 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 product candidates, including VS-6063 and VS-4718, that the development of the Company's product candidates will take longer or cost more than planned, and that the Company's product candidates 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, 2013 and in any subsequent SEC filings. The forward-looking statements contained in this press release 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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