Verastem Oncology Presents Duvelisib Data at EHA 2018 Annual Meeting

June 16, 2018

Phase Ib/II study of duvelisib in combination with FCR (dFCR) achieves ORR of 94% and 76% bone marrow MRD negativity in frontline therapy in younger CLL patients

Duvelisib demonstrates robust clinical activity in CLL with 73% ORR and a median of 15 month PFS in the DUO crossover study of patients who became relapsed/refractory to ofatumumab in DUO™

Additional data support the hypothesis that duvelisib, a first-in-class dual inhibitor of PI3K delta/gamma, targets malignant B-cells directly and modulates the tumor microenvironment

BOSTON--(BUSINESS WIRE)--Jun. 16, 2018-- Verastem, Inc. (Nasdaq: VSTM), the Company or Verastem Oncology, a biopharmaceutical company focused on developing and commercializing medicines to improve the survival and quality of life of cancer patients, today announced one oral and three poster presentations at the 23rd Congress of the European Hematology Association (EHA) being held June 14-17, 2018 in Stockholm, Sweden.

Data were presented on the Company's lead product candidate, duvelisib, a first-in-class oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma. An oral presentation by Dr. Matthew Davids, Dana-Farber Cancer Institute, highlighted the latest data from a Phase Ib/II study evaluating duvelisib in combination with FCR (dFCR) as a frontline treatment in younger patients with chronic lymphocytic leukemia (CLL). Three poster presentations highlighted additional duvelisib data, including crossover extension results from the Phase 3 DUO™ study in patients with relapsed or refractory CLL/small lymphocytic lymphoma (SLL), and new biomarker analyses on the tumor microenvironment modulation from the DUO™ study and the Phase 2 DYNAMO™ study in patients with refractory indolent non-Hodgkin lymphoma (iNHL), and the dual PI3K-delta and PI3K-gamma activity of duvelisib in the CONTEMPO™ study in patients with untreated follicular lymphoma (FL) who are treated with duvelisib in combination with CD20 antibody immunotherapy.

"Dr. Matthew Davids gave an oral presentation of new clinical data from the ongoing Phase Ib/II study evaluating duvelisib in combination with FCR (chemo-immunotherapy) in younger, fit CLL patients," said Diep Le, MD, PhD, Chief Medical Officer of Verastem Oncology. "The combination regimen achieved an overall response rate (ORR) of 94%, including 26% of patients experiencing a complete response or complete response with incomplete blood count recovery (CR/CRi), and 68% achieving a partial response. In addition, patients also experienced a high rate of bone marrow MRD negativity of 76%, which is significantly higher than historical data with FCR. Importantly, the results from this study demonstrated that duvelisib can be combined with a triple chemo-immunotherapy in the front-line setting with an acceptable safety profile".

Dr. Le added, "In addition, the DUO crossover extension data presented build upon the previously reported positive Phase 3 DUO study results and further support duvelisib's potential as an oral treatment option for patients with relapsed or refractory CLL/SLL. Post-crossover, oral duvelisib monotherapy demonstrated robust clinical activity with a 73% overall response rate (ORR) and a 15-month median PFS in the 89 patients that had previously received ofatumumab on DUO and subsequently progressed. Duvelisib monotherapy also demonstrated a manageable safety profile, with results from this study consistent with the well-characterized safety profile of duvelisib monotherapy in previous studies. It is encouraging to see such a robust response to duvelisib monotherapy, similar to response observed in the parent DUO study, in patients that had failed an additional line of therapy and needed a new treatment option. Collectively, the data presented at EHA this year continue to provide important insights to guide the future clinical development of duvelisib across a wide range of hematologic malignancies, both as a monotherapy and in combination with other agents."

Jonathan Pachter, PhD, Chief Scientific Officer of Verastem Oncology, commented, "The results presented by Drs. Casulo and Weaver continue to provide important evidence that the dual inhibition of PI3K-δ and PI3K-γ by duvelisib potentially yields added clinical benefit for CLL/SLL and FL patients by targeting both malignant B cells and the supportive tumor microenvironment. For example, these data indicate that duvelisib significantly inhibits chemokines from both cancer cells and the tumor microenvironment, and specifically, PI3K-γ inhibition impairs function of cancer-supportive macrophages and T cells."

Details for the EHA 2018 presentation and posters are as follows:

Oral Presentation

Title: A Phase IB/II Study of duvelisib in combination with FCR (dFCR) for Frontline Therapy of Younger CLL Patients
Lead author: Dr. Matthew Davids, Dana-Farber Cancer Institute
Final Abstract Code: S807
Summary: FCR is a common initial therapy for younger CLL patients; however, only about 20% will achieve a CR/CRi with minimum residual disease (MRD) negativity in the bone marrow (BM-MRD-). Oral duvelisib had previously shown promising efficacy in CLL, and therefore, the purpose of this study was to investigate the safety and rate of CR/CRi with BM-MRD- following treatment with dFCR. This Phase Ib/II study utilized a standard 3 + 3 design and included 2 dose levels of oral duvelisib (25mg once daily or 25mg twice daily). Duvelisib was given for 1 week with FCR added on Day 8. Up to 6 cycles of dFCR were administered, followed by up to 2 years of duvelisib maintenance.

Among the 31 patients evaluable for post-dFCR response, the ORR was 94%, with 26% achieving a CR (n=4) or CRi (n=4), and 68% achieving a partial response (PR). The best rate of MRD- in the BM in patients with at least one evaluation was 81% (25 of 31). All patients who achieved CR/CRi at primary endpoint were also BM-MRD- (26%). Among survivors, the median follow-up is 24.5 months (range 6.9-46). Two-year progression-free survival and overall survival are both 97%. Eight patients have now completed two years of duvelisib maintenance therapy. The most common all grade non-hematologic adverse events were nausea (72%, all Grade 1/2), fatigue (69%, 3% Grade 3), fever (53%, all Grade 1/2), diarrhea (47%, 3% Grade 3), transaminitis (34%, 28% Grade 3/4), anorexia (34%, all Grade 1/2), vomiting (28%, all Grade 1/2), pruritus (16%, 3% Grade 3), arthritis (9%,

all Grade 2) and CMV reactivation (6%, both Grade 2). The most common all grade hematologic adverse events were thrombocytopenia (65%; 34% Grade 3-4), neutropenia (59%; 50% Grade 3-4), and anemia (38%, 16% Grade 3). Serious AEs included transaminitis (n=9, including 5 Grade 3, 4 Grade 4), febrile neutropenia (n=6, all Grade 3), pneumonia (n=6, including 3 cases of PJP despite planned prophylaxis), and colitis (n=2, including 1 Grade 2 and 1 Grade 3). Based on these results the recommended Phase 2 dose of duvelisib in combination with FCR was 25mg twice daily. These results support the thesis that dFCR is an effective regimen for the initial therapy of younger, fit CLL patients and results in a high 81% rate of BM-MRD negativity, significantly higher than historical data with FCR; however infectious and immune-mediated toxicities were observed.

A copy of the oral presentation is available **here**.

Poster Presentations

Title: The Efficacy of Duvelisib Monotherapy Following Disease Progression on Ofatumumab Monotherapy in Patients with Relapsed/Refractory CLL or SLL in a Phase 3 Crossover Extension Study
Lead author: Dr. Peter Hillman, St. James University Hospital, Leeds, UK
Final Abstract Code: PF354
Summary: In the previously reported Phase 3 DUO™ study oral duvelisib monotherapy achieved a statistically significant improvement in median progression-free survival (mPFS) compared to ofatumumab in patients with relapsed or refractory CLL/ SLL (13.3 months versus 9.9 months, respectively; HR=0.52; p<0.0001), along with a manageable safety profile (Flinn, ASH 2017). The results reported here are from the open-label, DUO crossover extension study where patients with confirmed progressive disease (PD) following treatment with ofatumumab in DUO were given the option to receive treatment with duvelisib. Duvelisib 25mg BID was administered until PD, intolerance, death, or study withdrawal and responses were determined by investigators using modified IWCLL/IWG criteria.

Among the 89 evaluable patients (median three prior therapies (range 2-8), oral duvelisib monotherapy achieved a 73% overall response rate (ORR; 95% CI: 64, 82; 5% complete response with incomplete marrow recovery (CRis), 68% partial responses [PRs]) in the extension study. While on ofatumumab in the DUO study, these 89 patients had a 28% ORR (95% CI: 19, 37; 1% complete response (CR), 27% PRs). The mPFS for duvelisib in the extension study was 15 months (95% CI: 10, 17). While on ofatumumab in the DUO study, these 89 patients had a mPFS of 9 months (95% CI: 9, 11), per investigator's assessment. Notably, 83% of patients in the duvelisib arm post-crossover had >50% reductions in the size of their target nodal lesions. These same 89 patients had 27% reductions in the size of their target nodal lesions in the DUO ofatumumab arm. Median exposure to duvelisib in the extension study was 32 weeks. The safety profile of duvelisib monotherapy was manageable and consistent with what was observed in the Phase 3 DUO study. The most common Grade ≥3 treatment-emergent adverse events were neutropenia (22%), diarrhea (17%), colitis (9%), pneumonia (9%), rash (5%) and pyrexia (4%). These data build upon the previously reported positive DUO results and further support oral duvelisib monotherapy as an effective oral treatment option for patients with relapsed or refractory CLL/SLL.

A copy of the poster presentation will be available **here**.

Title: The effect of duvelisib, a dual inhibitor of PI3K-δ,γ, on components of the tumor microenvironment in previously untreated follicular lymphoma
Lead author: Dr. Carla Casulo, University of Rochester, Wilmot Cancer Center
Final Abstract Code: PF646
Summary: In previously reported data from the CONTEMPO trial, treatment-naive FL patients treated with duvelisib in combination with rituxumab had an ORR of 93% (36% CRR), and an ORR of 89% (41% CRR) was observed for patients treated with duvelisib in combination with obinutuzumab. In this study, blood samples from healthy volunteers and FL patients treated in the CONTEMPO study, both pre- and post-duvelisib treatment, were analyzed. Ex vivo and in vitro PI3K-γ assays and PI3K-δ assays, with PI3K-δ-selective (idelalisib, TGR-1202, IPI-3063) and PI3K-γ-selective (IPI-549) inhibitors were compared.

Duvelisib and idelalisib potently inhibited LPS-induced human monocytes via PI3K-δ, compared with the PI3K-γ selective IPI-549. For TGR-1202, the IC50 was below the recommended Phase 2 dose (RP2D) clinical exposure. Duvelisib and IPI-549 potently inhibited PI3K-γ dependent fMLP-stimulated human monocytes compared to idelalisib and TGR-1202. In FL patients treated with duvelisib, these PI3K-γ and PI3K-δ selective assays were inhibited 1-4 hours post treatment. Consistent with a PI3K-γ mechanism, both duvelisib and IPI-549 inhibited macrophage polarization to M2, reduced CXCL12-induced macrophage migration, and blocked CXCL12-induced T cell migration, which was not observed with PI3K-δ inhibitor IPI-3063. Collectively, these results support the thesis that duvelisib disrupts PI3K- δ,γ function in FL patients inhibiting the TME through cancer-supportive macrophages and T cells.

A copy of the poster presentation will be available **here**.

Title: Duvelisib inhibition of chemokines in patients with CLL (DUO study) and iNHL (DYNAMO study).
Lead author: Dr. David Weaver, Verastem Oncology
Final Abstract Code: PF649
Summary: PI3K-δ inhibition directly targets proliferation and survival of malignant leukemia and lymphoma cells, while PI3K-γ inhibition modulates the TME through key support cells, including tumor-associated macrophages, nurse-like stroma and T cells, and via soluble factors stimulating tumor growth, survival and migration. Serum samples from patients in the Phase 3 DUO study in relapsed/refractory CLL/SLL and the Phase 2 DYNAMO study in relapsed/refractory indolent NHL were collected at baseline and at C2D1 and used for correlative studies of 24 chemokines, cytokines and serum factors.

In serum samples from the DUO study, CCL1, CCL17, CXCL9, CXCL10, CXCL11, and IL-10 were reduced in patients treated with duvelisib (median 43.8%) but not in those treated with ofatumumab (p≤0.0009). Eight chemokines were reduced in both treatment arms, but the level of reduction was significantly greater for duvelisib-treated patients (median 64.6% for duvelisib versus 26.8% for ofatumumab [p≤0.001]). Many of the chemokines inhibited following duvelisib treatment are associated with the TME, including TNFα, IL-10, IL2Rα, IL12P40, CCL1, CCL17, CCL19, CXCL9, CXCL10, CXCL11, and CXCL13. In serum samples from the DYNAMO study, 13 corresponding chemokines were also inhibited (p≤0.008), including TME factors. Reductions occurred rapidly (by C2D1) in both studies. In DUO, there was a correlation between duration of response and reduction of the following chemokines: CCL17, CXCL11, IL-6, TRAIL, VEGF-D and TPO. These data support the hypothesis that treatment with duvelisib results in significant reduction of chemokines potentially derived from the tumor cells and TME and that further investigation of the effects of duvelisib on TME pharmacodynamic markers is warranted.

A copy of the poster presentation will be available **here**.

About Duvelisib

Duvelisib is a first-in-class investigational oral, dual inhibitor of phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma, two enzymes known to help support the growth and survival of malignant B-cells and T-cells. PI3K signaling may lead to the proliferation of malignant B- and T-cells and is thought to play a role in the formation and maintenance of the supportive tumor microenvironment.[1,2,3] Duvelisib was evaluated in late- and mid-stage extension trials, including DUO™, a randomized, Phase 3 monotherapy study in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL),[4] and DYNAMO™, a single-arm, Phase 2 monotherapy study in patients with refractory indolent non-Hodgkin lymphoma (iNHL).[5] Both DUO and DYNAMO achieved their primary endpoints. Verastem Oncology's New Drug Application (NDA) requesting the full approval of duvelisib for the treatment of patients with relapsed or refractory CLL/SLL, and accelerated approval for the treatment of patients with relapsed or refractory follicular lymphoma (FL) was accepted for filing by the U.S. Food and Drug Administration (FDA), granted Priority Review and assigned a target action date of October 5, 2018. Duvelisib is also being developed by Verastem Oncology for the treatment of peripheral T-cell lymphoma (PTCL), and is being investigated in combination with other agents through investigator-sponsored studies.[6] Information about duvelisib clinical trials can be found on www.clinicaltrials.gov.

About Verastem Oncology

Verastem, Inc. (Nasdaq:VSTM), operating as Verastem Oncology, is a biopharmaceutical company focused on developing and commercializing medicines to improve the survival and quality of life of cancer patients. Verastem Oncology is currently developing duvelisib, a dual inhibitor of PI3K-delta and PI3K-gamma, which has successfully met its primary endpoint in a Phase 2 study in indolent Non-Hodgkin Lymphoma (iNHL) and a Phase 3 clinical trial in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Verastem Oncology's New Drug Application (NDA) requesting the full approval of duvelisib for the treatment of patients with relapsed or refractory CLL/SLL, and accelerated approval for the treatment of patients with relapsed or refractory follicular lymphoma (FL) was accepted for filing by the U.S. Food and Drug Administration (FDA), granted Priority Review and assigned a target action date of October 5, 2018. In addition, Verastem Oncology is developing the FAK inhibitor defactinib, which is currently being evaluated in three separate clinical collaborations in combination with immunotherapeutic agents for the treatment of several different cancer types, including pancreatic cancer, ovarian cancer, non-small-cell lung cancer (NSCLC), and mesothelioma. Verastem Oncology's product candidates seek to treat cancer by modulating the local tumor microenvironment and enhancing anti-tumor immunity. For more information, please visit www.verastem.com.

Forward-looking statements notice:

This press release includes forward-looking statements about Verastem Oncology's strategy, future plans and prospects, including statements regarding the development and activity of Verastem Oncology's investigational product candidates, including duvelisib and defactinib, and Verastem Oncology's PI3K and FAK programs generally, the structure of our planned and pending clinical trials, Verastem Oncology's financial guidance and the timeline and indications for clinical development and regulatory submissions. The words "anticipate," "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 approval of Verastem Oncology's New Drug Application for duvelisib will not occur on the expected timeframe or at all, including by the U.S. Food and Drug Administration's target action date; that a filing of a European Marketing Application may not be achieved in fiscal year 2019 or at all; that even if data from clinical trials is positive, regulatory authorities may require additional studies for approval or may approve for indications or patient populations that are not as broad as intended and the product may not prove to be safe and effective or may require labeling with use or distribution restrictions; that the preclinical testing of Verastem Oncology'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 the full data from the DUO study will not be consistent with the previously presented results of the study; that data may not be available when expected, including for the Phase 3 DUO study; that the degree of market acceptance of product candidates, if approved, may be lower than expected; that the timing, scope and rate of reimbursement for our product candidates is uncertain; that there may be competitive developments affecting our product candidates; that data may not be available when expected; that enrollment of clinical trials may take longer than expected; that our product candidates will cause unexpected safety events or result in an unmanageable safety profile as compared to their level of efficacy; that duvelisib will be ineffective at treating patients with lymphoid malignancies; that Verastem Oncology will be unable to successfully initiate or complete the clinical development and eventual commercialization of its product candidates; that the development and commercialization of Verastem Oncology's product candidates will take longer or cost more than planned; that Verastem Oncology may not have sufficient cash to fund its contemplated operations; that Verastem Oncology or Infinity Pharmaceuticals, Inc. will fail to fully perform under the duvelisib license agreement; that Verastem Oncology may be unable to make additional draws under its debt facility or obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity, debt financing or otherwise; that Verastem Oncology will not pursue or submit regulatory filings for its product candidates, including for duvelisib in patients with CLL/SLL or iNHL; and that Verastem Oncology's product candidates will not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients. 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, 2017 as filed with the Securities and Exchange Commission (SEC) on March 13, 2018 and in any subsequent filings with the SEC. The forward-looking statements contained in this press release reflect Verastem Oncology's views as of the date hereof, and the Company does not assume and specifically disclaims any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by law.

References

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[2] Reif K et al. Cutting Edge: Differential Roles for Phosphoinositide 3 kinases, p110-gamma and p110-delta, in lymphocyte chemotaxis and homing. J Immunol 2004:173:2236-2240.

[3] Schmid M et al. Receptor Tyrosine Kinases and TLR/IL1Rs Unexpectedly activate myeloid cell PI3K, a single convergent point promoting tumor inflammation and progression. Cancer Cell 2011;19:715-727.

[4] www.clinicaltrials.gov, NCT02004522

[5] www.clinicaltrials.gov, NCT01882803

[6] www.clinicaltrials.gov, NCT02783625, NCT02158091

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Verastem Oncology
Marianne M. Lambertson, +1 781-292-4273
Vice President, Corporate Communications
Investor Relations/Public Relations
mlambertson@verastem.com