Researchers Present Preclinical Data Showing Synergistic Activity of SpringWorks Therapeutics' Gamma Secretase Inhibitor (Nirogacestat) with GlaxoSmithKline's BCMA Antibody-Drug Conjugate (Belantamab Mafodotin) at the American Society of Hematology (ASH)

December 9, 2019

STAMFORD, Conn., Dec. 09, 2019 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a clinical-stage biopharmaceutical company focused on developing life-changing medicines for patients with severe rare diseases and cancer, today announced that its collaborator, GlaxoSmithKline, presented data evaluating SpringWorks' investigational gamma secretase inhibitor (GSI), nirogacestat (formerly PF-03084014), alone and in combination with GlaxoSmithKline's investigational anti-B-cell maturation antigen (BCMA) antibody-drug conjugate (ADC), belantamab mafodotin (formerly GSK2857916), in preclinical cell line models of human multiple myeloma and other lymphomas. The data demonstrated that treatment of BCMA-expressing cancer cell lines with nirogacestat led to significantly increased levels of cell surface expression of BCMA and corresponding decreases in shedding of BCMA, as measured by levels of soluble BCMA. Further, the combination of nirogacestat and belantamab mafodotin resulted in synergistic increases in cancer cell killing as compared to belantamab mafodotin alone, with an up to ~3,000-fold improvement in cytotoxicity. The data were presented in a poster presentation at the 61st American Society of Hematology (ASH) Annual Meeting and Exposition.[1]

"The data presented at ASH support the potential of nirogacestat to serve as a meaningful potentiator of BCMA-directed therapies," said Saqib Islam, Chief Executive Officer of SpringWorks. "We look forward to further evaluating the combination of nirogacestat and belantamab mafodotin in the clinic as we work to fully explore the role of nirogacestat in multiple myeloma and other BCMA-expressing cancer types."

As previously announced, GlaxoSmithKline will sponsor and conduct a Phase 1b clinical trial to evaluate the safety, tolerability and preliminary efficacy of nirogacestat in combination with belantamab mafodotin in patients with relapsed or refractory multiple myeloma. This combination will be part of DREAMM-5, a platform trial being conducted by GlaxoSmithKline that is evaluating multiple belantamab mafodotin-containing combinations in separate sub-studies.[2] SpringWorks expects the Phase 1b clinical trial of nirogacestat in combination with belantamab mafodotin to be initiated in the first quarter of 2020.

Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with Nirogacestat (PF-03084014, gamma-secretase inhibitor) in BCMA-Expressing Cancer Cell Lines: Poster No. 4401

In a poster presentation at ASH, GlaxoSmithKline scientists presented findings from a preclinical study aimed at further enhancing belantamab mafodotin activity in BCMA-expressing cancer cell lines. The researchers sought to increase cell surface levels of BCMA by blocking shedding of BCMA using nirogacestat and to evaluate this effect on the activity of belantamab mafodotin by combining it with nirogacestat across a panel of human cancer cell lines.

A 3-day proliferation assay on a panel of multiple myeloma and lymphoma cell lines with varying levels of BCMA expression was conducted. Results showed that adding nirogacestat enhanced multiple myeloma cell killing activity of belantamab mafodotin up to 3,000-fold and enabled sensitivity in belantamab mafodotin resistant cell lines outside of multiple myeloma. In a 24-hour assay to measure antibody-dependent cellular cytotoxicity (ADCC) activity, the study also showed increased effector function when combining nirogacestat with a BCMA monoclonal antibody.

A Phase 1b clinical trial evaluating belantamab mafodotin in combination with nirogacestat in patients with relapsed or refractory multiple myeloma will be examined as a sub-study in GlaxoSmithKline's DREAMM-5 platform trial.

About Nirogacestat

Nirogacestat is an oral, selective, small molecule gamma-secretase inhibitor in Phase 3 clinical development for the treatment of desmoid tumors, which are rare and often debilitating and disfiguring soft-tissue tumors. Gamma secretase cleaves multiple transmembrane protein complexes, including Notch, which is believed to play a role in activating pathways that contribute to desmoid tumor growth.

In addition, gamma secretase has been shown to directly cleave membrane-bound BCMA, resulting in the release of the BCMA extracellular domain, or ECD, from the cell surface. By inhibiting gamma secretase, membrane-bound BCMA can be preserved, increasing target density while reducing levels of soluble BCMA ECD, which may serve as decoy receptors for BCMA-directed therapies. Nirogacestat's ability to enhance the activity of BCMA-directed therapies has been observed in preclinical models of multiple myeloma.

Nirogacestat has received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) for the treatment of desmoid tumors (June 2018) and from the European Commission for the treatment of soft tissue sarcoma (September 2019). The FDA also granted Fast Track and Breakthrough Therapy Designations for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis (November 2018 and August 2019).

About belantamab mafodotin (GSK2857916)
Belantamab mafodotin is an investigational anti-B-cell maturation antigen (BCMA) antibody-drug conjugate in clinical development for patients with relapsed/refractory multiple myeloma and other advanced hematologic malignancies expressing BCMA.

In 2017, belantamab mafodotin was awarded Breakthrough Therapy designation from the U.S. Food and Drug Administration and PRIME designation from the European Medicines Agency; these designations are intended to facilitate development of investigational medicines that have shown clinical promise for conditions where there is significant unmet need.

About SpringWorks Therapeutics

SpringWorks is a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing

life-changing medicines for underserved patient populations suffering from devastating rare diseases and cancer. SpringWorks has a differentiated portfolio of small molecule targeted oncology product candidates and is advancing two potentially registrational clinical trials in rare tumor types, as well as several other programs addressing highly prevalent, genetically defined cancers. SpringWorks' strategic approach and operational excellence in clinical development have enabled it to rapidly advance its two lead product candidates into late-stage clinical trials while simultaneously entering into multiple shared-value partnerships with industry leaders to expand its portfolio. For more information, please visit www.springworkstx.com.

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Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding SpringWorks' clinical trials and its strategy, business plans and focus. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, those related to the timing for completion of SpringWorks' clinical trials of its product candidates, whether and when, if at all, SpringWorks' product candidates will receive approval from the U.S. Food and Drug Administration, or FDA, or other foreign regulatory authorities, competition from other biopharmaceutical companies, and other risks identified in the section entitled "Risk Factors" in Item 1A of Part II of SpringWorks' Quarterly Report on Form 10-Q for the quarter ended September 30, 2019, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings with the Securities and Exchange Commission. SpringWorks cautions you not to place undue reliance on any forward-looking statements, which speak only as of the date they are made. SpringWorks disclaims any obligation to publicly update or revise any such statements to reflect any change in expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements. Any forward-looking statements contained in this press release represent SpringWorks' views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date.

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References:

[1] Eastman, S., Shelton, C., Gupta, I., Krueger, J., Blackwell, C., & Bojczuk, P. M. (2019, December). *4401 Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with PF-03084014 (gamma-secretase inhibitor) in Bcma-Expressing Cancer Cell Lines*. Poster session presented at the 61st American Society of Hematology Annual Meeting & Exposition, Orlando, FL.

[2] Richardson, P.G., Biswas, S., Holkova, B., Jackson, N., Netherway, T., Bao, W., …Opalinksa, J. (2019, December)*1857 Dreamm-5: Platform Trial Evaluating Belantamab Mafodotin (a BCMA-directed Immuno-conjugate) in Combination with Novel Agents in Relapsed or Refractory Multiple Myeloma (RRMM).* Poster session presented at the 61st American Society of Hematology Annual Meeting & Exposition, Orlando, FL.