SpringWorks Therapeutics Announces Dosing of First Patient in Phase 2 Trial Evaluating Nirogacestat in Patients with Ovarian Granulosa Cell Tumors

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STAMFORD, Conn., Sept. 29, 2022 (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 the first patient has been dosed in a Phase 2 trial evaluating nirogacestat, SpringWorks' investigational gamma secretase inhibitor, as a monotherapy in patients with recurrent ovarian granulosa cell tumors.

Ovarian granulosa cell tumors account for approximately 5% of all ovarian cancers and are the most common subtype of ovarian sex cord tumors, representing 70% of all cases. Nearly all ovarian granulosa cell tumors harbor a mutation in the *FOXL2* gene and preclinical studies have demonstrated that ovarian granulosa cell tumor cell lines are susceptible to gamma secretase inhibition.[1,2]

"The science behind this study is exciting because Notch signaling, a key target of gamma secretase inhibitors, is involved in the expression of FOXL2, which is an integral component of granulosa cell development, proliferation, and function," said Panos Konstantinopoulos, M.D., Ph.D., Director of Gynecological Oncology Translational Research at Dana-Farber Cancer Center and Harvard Medical School and the Principal Investigator of the Phase 2 trial. "Without any FDA-approved therapies, there is a high unmet need for patients with recurrent ovarian granulosa cell tumors and I look forward to evaluating nirogacestat in this important study."

"Over the course of their disease, patients with ovarian granulosa cell tumors may experience severe abdominal pain associated with a large pelvic or abdominal mass, requiring surgery and subsequent systemic therapy," said Saqib Islam, Chief Executive Officer of SpringWorks. "We are pleased to be developing a much-needed therapy for these patients and are encouraged by this new, meaningful opportunity for nirogacestat."

The Phase 2 trial (NCT05348356) is a multi-center, single-arm, open-label study evaluating the efficacy, tolerability, safety, and pharmacokinetics of nirogacestat in patients with recurrent ovarian granulosa cell tumors. The study will enroll approximately 40 patients who will receive 150mg of nirogacestat twice daily. Eligible patients will have recurrent ovarian granulosa cell tumors and will have received one or more prior lines of systemic therapy. The primary endpoint of the trial is objective response rate as measured by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Secondary endpoints include progression-free survival, overall survival, duration of response, safety and tolerability, and quality of life assessments.

About Ovarian Granulosa Cell Tumors

Ovarian granulosa cell tumors (OvGCT) are a rare ovarian cancer subtype that are usually slow-growing tumors. OvGCT account for approximately 5% of all ovarian cancers and are the most common subtype of ovarian sex cord stromal tumors. At the time of diagnosis, patients typically present with severe abdominal pain, abdominal distension, and abnormal or postmenopausal bleeding alongside a large pelvic or abdominal mass.[3]

OvGCT are most commonly diagnosed in women during the perimenopausal/early postmenopausal period with a median age of diagnosis of 50 years.[3] It is estimated that there are 1,500 to 2,000 new cases diagnosed per year in the U.S., and an estimated prevalence of approximately 10,000-15,000 patients with OvGCT in the U.S.[4,5] Prognosis for patients with advanced disease is poor, with a 10-year survival rate of approximately 25%.[6]

There are currently no FDA-approved therapies for patients with OvGCT. Surgery is currently the mainstay of initial treatment, however, the risk of recurrence is high for those with advanced disease and off-label systemic therapy, including chemotherapy, is often used.

About Nirogacestat

Nirogacestat is an investigational, oral, selective, small molecule gamma secretase inhibitor in Phase 3 clinical development for desmoid tumors and in Phase 2 clinical development for ovarian granulosa cell tumors. Gamma secretase cleaves multiple transmembrane protein complexes, including Notch, which is believed to play a role in activating pathways that contribute to growth of desmoid and ovarian granulosa cell tumors.

In addition, gamma secretase has been shown to directly cleave membrane-bound B cell maturation antigen (BCMA), resulting in the release of the BCMA extracellular domain (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. SpringWorks is evaluating nirogacestat as a BCMA potentiator and has eight collaborations with industry-leading BCMA developers to evaluate nirogacestat in combinations across modalities, including with an antibody-drug conjugate, two CAR T cell therapies, three bispecific antibodies and a monoclonal antibody. SpringWorks has also formed research collaborations with Fred Hutchinson Cancer Research Center and Dana-Farber Cancer Institute to further characterize the ability of nirogacestat to modulate BCMA and potentiate BCMA-directed therapies using a variety of preclinical multiple myeloma models.

Nirogacestat has received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) for the treatment of desmoid tumors and from the European Commission for the treatment of soft tissue sarcoma. 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. SpringWorks plans to submit a New Drug Application (NDA) to the FDA in the second half of 2022, which will be submitted for review under the FDA's Real-Time Oncology Review (RTOR) program.

About SpringWorks Therapeutics

SpringWorks is a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for patients living with severe rare diseases and cancer. SpringWorks has a differentiated targeted oncology pipeline spanning solid tumors and hematological cancers, including two potentially registrational clinical trials in rare tumor types as well as several 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 innovators in industry and academia to unlock the full potential for its portfolio and create more solutions for patients with cancer. For more information, visit www.springworkstx.com and follow @SpringWorksTx on Twitter and LinkedIn.

SpringWorks Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, relating to our business, operations, and financial conditions, including, but not limited to, current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, the timing of our planned NDA submission for nirogacestat, and our plans for seeking regulatory approval for and making nirogacestat available to desmoid tumor patients, if approved, as well as relating to other future conditions. Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. 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, risks relating to: (i) the success and timing of our product development activities, including the initiation and completion of SpringWorks' clinical trials, (ii) the fact that topline or interim data from a clinical study may not be predictive of the final or more detailed results of such study, or the results of other ongoing or future studies, (iii) the success and timing of our collaboration partners' ongoing and planned clinical trials, (iv) the timing of our planned regulatory submissions and interactions, including the NDA for nirogacestat planned for the second half of 2022 and the timing and outcome of decisions made by the U.S. Food and Drug Administration (FDA) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; (v) whether FDA or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our drug candidates, including nirogacestat and mirdametinib, (vi) our ability to obtain and maintain regulatory approval of any of our product candidates, (vii) our plans to research, discover and develop additional product candidates, (viii) our ability to enter into collaborations for the development of new product candidates, (ix) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, (x) our ability to meet any specific milestones set forth herein, and (xi) uncertainties and assumptions regarding the impact of the COVID-19 pandemic on SpringWorks' business, operations, clinical trials, supply chain, strategy, goals and anticipated timelines.

Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between SpringWorks' expectations and actual results, you should review the "Risk Factors" in Item 1A of Part I of SpringWorks' Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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