SpringWorks Therapeutics Announces Phase 1b/2a Clinical Trial of Mirdametinib in Patients with Advanced Solid Cancers Harboring MAPK-Activating Mutations

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Platform Study to Evaluate Mirdametinib as a Combination Therapy with Fulvestrant in Patients with ER+ Metastatic Breast Cancer and as a Monotherapy in Patients with Advanced Solid Tumors Harboring Activating Mutations in MEK1 or MEK2

STAMFORD, Conn., Aug. 03, 2021 (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 Company will be evaluating mirdametinib, an investigational MEK inhibitor, in a platform study sponsored by Memorial Sloan Kettering Cancer Center (MSK) and supported by SpringWorks exploring the compound both as a monotherapy and as a combination therapy in advanced solid tumors harboring MAPK-activating mutations. The trial, which is expected to begin recruiting patients during the third quarter of 2021, will initially explore mirdametinib in two patient cohorts: the first in combination with fulvestrant, a selective estrogen receptor degrader (SERD) in patients with estrogen receptor positive (ER+) metastatic breast cancer (mBC) with MAPK alterations (particularly inactivating mutations in *NF1*), and as a monotherapy in advanced solid tumors harboring oncogenic *MEK1* or *MEK2* mutations.

“Emerging evidence points to alterations in the MAPK pathway playing a key role in mediating resistance to hormone therapy in ER+ mBC, which represents a significant unmet medical need,” explained Ezra Rosen, M.D., Ph.D., Medical Oncologist, Assistant Member of MSK’s Early Drug Development Service, and the study’s principal investigator. “Based on emerging preclinical data, combinations of MAPK pathway inhibitors with ER-targeted therapy could potentially address this resistance mechanism and we look forward to studying mirdametinib to evaluate whether this MEK inhibitor can provide a clinical benefit. Separately, given the preclinical evidence that activating mutations in *MEK1* and *MEK2* can also act as oncogenic drivers in cancer, we’re looking to explore a potential role for mirdametinib monotherapy in solid tumors harboring these driver mutations.”

Approximately 70% of breast cancers are ER+. Hormonal therapies targeting ER, such as SERDs, can be effective in treating ER+ mBC, but over 90% of patients eventually develop resistance to ER-targeted therapy. Loss of NF1 function has been shown to be responsible for enhanced ER transcriptional activity and reduced sensitivity to fulvestrant in preclinical models, with up to 6% of ER+ mBC patients harboring a detectable *NF1* mutation.[1] Combinations of MAPK pathway inhibitors and ER-targeted therapy could potentially address this resistance, as demonstrated by a combination of a MEK inhibitor and fulvestrant showing anti-tumor activity in fulvestrant-refractory NF1-deficient ER+ mBC preclinical models.[1,2]

In addition, *MEK1* and *MEK2* mutations are present in up to 2% of solid tumors and have been validated as oncogenic drivers. Recent publications demonstrate the activity of MEK inhibitors, including mirdametinib, in preclinical models driven by a subset of these MEK mutations.[3,4]

“This biomarker-driven platform study will enable us to evaluate mirdametinib’s ability to address subsets of patients with solid tumors that harbor specific MAPK pathway mutations,” said Mike Burgess, M.B.Ch.B., Ph.D., Head of Research and Development at SpringWorks. “We are committed to exploring the full potential of mirdametinib on behalf of patients with devastating cancers and look forward to collaborating with Dr. Rosen and his colleagues at MSK on this important trial.”

About the MSK-Sponsored Phase 1b/2a Trial

The open-label Phase 1b/2a parallel design, platform study will evaluate the safety and tolerability, efficacy, and pharmacokinetics of mirdametinib in two study arms: (1) in combination with fulvestrant in postmenopausal patients with ER+ mBC harboring *NF1* loss of function or other alterations of the MAPK pathway and (2) as a monotherapy in adult patients with advanced solid cancers driven by the alterations of the MAPK pathway, including *MEK1* or *MEK2* mutations.

The primary objectives of the trial will be to evaluate the safety and tolerability and anti-tumor efficacy of mirdametinib in combination with fulvestrant and as a single agent. The efficacy endpoints will include best objective response by RECIST 1.1, disease control rate, duration of response, progression-free survival, and pharmacokinetic endpoints. Biomarker analyses will also be conducted to evaluate the changes from baseline in the biomarkers of tumor biology and anti-tumor activity and characterize potential mechanisms of resistance.

About Mirdametinib

Mirdametinib is an oral, potent, allosteric, brain-penetrant small molecule designed to inhibit MEK1 and MEK2, which are proteins that occupy pivotal positions in the MAPK pathway and that play a central role in multiple oncology and rare disease indications. To date, over 250 subjects have been exposed to treatment with mirdametinib across clinical trials, with preliminary evidence of clinical activity against tumors driven by over-activated MAPK signaling.[5]

Mirdametinib is being evaluated as a monotherapy in a Phase 2b trial for pediatric and adult patients with NF1-associated plexiform neurofibromas (NF1-PN), and in a Phase 1/2 trial for patients with pediatric low-grade gliomas. In addition, mirdametinib is being evaluated in a Phase 1b/2 trial in combination with BeiGene’s RAF dimer inhibitor, lifirafenib, in patients with advanced or refractory solid tumors harboring *RAS* mutations, *RAF* mutations, and other MAPK pathway aberrations.

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 portfolio of small molecule product candidates and is advancing 15 development programs, 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 expand its portfolio and create more solutions for patients with cancer. For more information, please visit www.springworkstx.com and follow @SpringWorksTx on Twitter and LinkedIn.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 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, and 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 interim data from a clinical study may not be predictive of the final 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) our ability to obtain and maintain regulatory approval of any of our product candidates, (v) our plans to research, discover and develop additional product candidates, (vi) our ability to enter into collaborations for the development of new product candidates, (vii) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, (viii) our ability to meet any specific milestones set forth herein, and (ix) 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 March 31, 2021, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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