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Syros Presents New Preclinical Data on SY-1365, Its First-in-Class Selective CDK7 Inhibitor, and Discovery of Potential New Drug Targets in Triple Negative Breast Cancer at San Antonio Breast Cancer Symposium

SY-1365 Shows Anti-Tumor Activity Across Broad Panel of Breast Cancer Cell Lines

Company Identifies Potential Biomarkers to Predict Response to SY-1365

Analysis of Regulatory Genome of Cancer Stem Cells in Triple Negative Breast Cancer Reveals Potential New Targets for Attacking Relapse and Metastasis

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS), a biopharmaceutical company pioneering the discovery and development of medicines to control the expression of disease-driving genes, today announced that new preclinical data on SY-1365, its first-in-class selective cyclin-dependent kinase 7 (CDK7) inhibitor currently in a Phase 1 clinical trial in advanced solid tumors, demonstrate anti-tumor activity across a broad panel of breast cancer cell lines and point to potential biomarkers predictive of response. The Company also announced its identification of key genes driving relapse and metastasis in triple negative breast cancer (TNBC), pointing to potential new drug targets. These data were presented at the San Antonio Breast Cancer Symposium (SABCS).

“These data speak to the power of our gene control platform to provide a new lens for understanding disease with important implications for developing much-needed therapies in defined subsets of patients,” Eric R. Olson, Ph.D., Chief Scientific Officer of Syros. “Despite advances in the treatment of certain cancers, two of the biggest challenges in cancer treatment remain the ability to pair the right patients with the right drugs and to prevent the emergence of drug resistance in response to targeted therapies. By analyzing regulatory regions of the genome, we discovered potential biomarkers of response to SY-1365 within heterogeneous patient populations that we can further explore during clinical development. Separately, using our platform, we also identified new potential points of therapeutic intervention in TNBC with the potential to thwart the mechanisms cancer uses to become resistant to therapy and spread to other parts of the body.”

New Preclinical Data on SY-1365

Syros scientists analyzed the anti-tumor activity of SY-1365 across a panel of more than 400 cancer cell lines, including 19 TNBC cell lines and 21 ER-positive, PR-positive and HER2-positive cells lines. They then grouped the cell lines according to sensitivity to SY-1365 and

looked for markers of response using Syros' gene control platform to analyze regulatory regions of the genome. The data showed:

- SY-1365 induced cell death in 15 out of the 19 TNBC cell lines and 17 of the 21 ER-positive, PR-positive and HER2-positive cells lines.
- Sensitivity to SY-1365 in these breast cancer cell lines was associated with a super-enhancer, a highly specialized regulatory region of the genome, that drives increased expression of the known oncogene *MYC*.
- Sensitivity to SY-1365 was also associated with low expression of the mitochondrial apoptosis antagonist *BCL2L1* in these cell lines.
- Lowered expression of *MCL1*, a gene in the mitochondrial apoptosis pathway known to inhibit apoptosis, was associated with SY-1365 target engagement and anti-tumor activity in cell lines and a cell-derived xenograft model of TNBC.

The Phase 1 trial of SY-1365 is a multi-center, open-label trial enrolling patients with advanced solid tumors. The primary objective of the trial is to assess the safety and tolerability of escalating doses of SY-1365, with the goal of establishing a maximum tolerated dose and a recommended Phase 2 dose and regimen. The dose-escalation phase is open and expected to enroll approximately 35 solid tumor patients for whom standard curative or palliative measures do not exist or are no longer effective. Following the dose-escalation phase, expansion cohorts are planned to further evaluate the safety and anti-tumor activity of SY-1365 in patients with transcriptionally driven tumors and to enroll patients with tumors of any histology in a cohort focused on analyzing biopsied tumor tissue. Additional details about the trial can be found using the identifier NCT03134638 at www.clinicaltrials.gov. Syros expects to present initial clinical data from this study in 2018.

Mechanisms of Relapse and Metastasis in TNBC

Using its gene control platform, Syros scientists, in collaboration with the lab of Robert Weinberg, Ph.D. at the Whitehead Institute, analyzed regulatory regions of the genome in cancer-stem cell enriched TNBC cell lines. Cancer stem cells (CSCs) are known to be involved in resistance to chemotherapies, relapse of disease and development of metastasis. The analysis revealed key genes that may be involved in driving disease relapse and metastasis, with implications for the discovery and development of novel therapies for TNBC. Notably, *TP73* was found to be a core driver of transcriptional circuitry in CSCs, controlling super-enhancer associated genes involved in cell migration, signal transduction and developmental processes. *TP73* is a gene that encodes a DNA-binding transcription factor called p73. The set of *TP73*-controlled genes provide new leads for drug discovery and development with potential to yield much-needed new therapies for TNBC patients.

About Syros Pharmaceuticals

Syros Pharmaceuticals is pioneering the understanding of the non-coding region of the genome to advance a new wave of medicines that control expression of disease-driving genes. Syros has built a proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA in human disease tissue to identify and drug novel targets linked to genomically defined patient populations. Because gene expression is fundamental to the function of all cells, Syros' gene control platform has broad potential to create medicines that achieve profound and durable benefit across a range of diseases. Syros is currently focused on cancer and immune-mediated diseases and is advancing a

growing pipeline of gene control medicines. Syros' lead drug candidates are SY-1425, a selective RARα agonist in a Phase 2 clinical trial for genomically defined subsets of patients with acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective CDK7 inhibitor in a Phase 1 clinical trial for patients with advanced solid tumors, including transcriptionally dependent cancers such as triple negative breast, small cell lung and ovarian cancers. Led by a team with deep experience in drug discovery, development and commercialization, Syros is located in Cambridge, Mass.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including without limitation statements regarding the ability to identify biomarkers predictive of response to SY-1365, the therapeutic benefit of SY-1365 in patients with TNBC; the reporting of initial clinical data from the ongoing Phase 1 clinical trial of SY-1365 in 2018; the ability to validate *TP73*-controlled genes as targets for therapeutic intervention and the ability to identify suitable drug candidates that modulate those genes; and the benefits of Syros' gene control platform. The words ''anticipate,'' ''believe,'' ''continue,'' ''could,'' ''estimate,'' ''expect,'' ''intend,'' ''may,'' ''plan,'' ''potential,'' ''predict,'' ''project,'' ''target,'' ''should,'' ''would,'' and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including Syros' ability to: advance the development of its programs, including SY-1425 and SY-1365, under the timelines it projects in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with the *RARA* and *IRF8* biomarkers; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; obtain and maintain necessary regulatory approvals; identify, enter into and maintain collaboration agreements with third parties; manage competition; manage expenses; raise the substantial additional capital needed to achieve its business objectives; attract and retain qualified personnel; and successfully execute on its business strategies; risks described under the caption "Risk Factors" in Syros' Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which is on file with the Securities and Exchange Commission; and risks described in other filings that Syros makes with the Securities and Exchange Commission in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Syros expressly disclaims any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

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