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Syros Presents New Preclinical PK and PD Data for SY-1365, Its First-in-Class Selective CDK7 Inhibitor, at AACR-NCI-EORTC Conference

SY-1365 Demonstrates Prolonged PD Effect and Anti-Tumor Activity in Multiple Preclinical Models of Cancer Using Intermittent Dosing, Providing Rationale for Twice Weekly Dosing Regimen Currently Being Used in Ongoing Phase 1 Clinical Trial

Data Support Use of CDK7 Target Occupancy in Patient Blood Samples as PD Marker in Ongoing Clinical Trial to Guide Optimization of Dose and Regimen for SY-1365

Publication in Cancer Discovery Highlights CDK7 Inhibition in Combination with Targeted Therapies as Promising Approach for Combatting Drug Resistance

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ:SYRS), a biopharmaceutical company pioneering the development of medicines to control the expression of disease-driving genes, today announced that new preclinical pharmacodynamic (PD) and pharmacokinetic (PK) data providing a rationale for the twice weekly dosing regimen currently being used in the ongoing Phase 1 clinical trial of SY-1365, its first-in-class selective cyclin-dependent kinase 7 (CDK7) inhibitor, in advanced solid tumors were presented at the 2017 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference in Philadelphia.

“We are encouraged by the preclinical PK and PD data for SY-1365,” said David A. Roth, M.D., Chief Medical Officer of Syros. “The prolonged PD effect, coupled with the sustained tumor regressions seen in multiple preclinical models of difficult-to-treat cancers using intermittent dosing, support investigation of a twice-a-week dosing regimen for patients. Additionally, based on the correlation between CDK7 target occupancy and the anti-tumor activity of SY-1365, we developed a PD marker for use in our ongoing Phase 1 trial that we believe will help us efficiently identify the optimal dose and regimen for SY-1365.”

Syros scientists evaluated the relationship between SY-1365’s PK, PD and anti-tumor activity in multiple *in vivo* models, including preclinical models of triple negative breast cancer (TNBC) and acute myeloid leukemia (AML), across a range of doses and regimens from daily to weekly dosing. SY-1365 is a covalent inhibitor that binds irreversibly to CDK7. The data showed:

- A prolonged PD effect, as measured by CDK7 target occupancy, with a half-life of about three days, supporting intermittent dosing.
- A dose-dependent relationship between CDK7 target occupancy and anti-tumor activity in a preclinical model of AML.

- Sustained tumor regressions in multiple *in vivo* models using a twice weekly dosing regimen consistent with the initial regimen in the ongoing Phase 1 clinical trial.
- CDK7 target occupancy in blood cells in preclinical models similar to that seen in tumor cells, supporting the use of an assay measuring target occupancy in patients' blood samples as a PD marker in the ongoing Phase 1 trial to help guide optimization of the dose and regimen to establish a recommended Phase 2 dose.

The Phase 1 trial of SY-1365 is a multi-center, open-label trial that is expected to enroll approximately 70 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 to 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 triple negative breast, small cell lung and ovarian cancers, to confirm a recommended Phase 2 dose and regimen, 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 also announced that a publication co-authored by two of its scientific founders Nathanael S. Gray, Ph.D., and Richard A. Young, Ph.D., in the peer-reviewed scientific journal *Cancer Discovery* (Rusan M., et al., "Suppression of adaptive responses to targeted cancer therapy by transcriptional repression") highlighted CDK7 inhibition in combination with targeted therapies as a promising new approach for combatting drug resistance. In multiple *in vitro* and *in vivo* models of treatment-resistant cancers, a research tool compound, known as THZ1, which inhibits CDK7, enhanced tumor cell killing and impeded the emergence of drug-resistant cell populations when combined with targeted therapies, including MEK, BRAF, EGFR and ALK inhibitors, compared to either THZ1 or the targeted therapy alone. These findings suggest that CDK7 inhibition prevents the formation of active enhancers that drive the increased expression of genes promoting the emergence of drug resistance in response to targeted therapy and blocks transcriptional programs required for the growth and survival of cancer.

Syros has an exclusive, worldwide license from the Dana-Farber Cancer Institute under certain patents relating to CDK7 inhibitors, including THZ1. Using its internal drug discovery capabilities, Syros generated SY-1365 to have better drug-like properties than THZ1, making it suitable for clinical development.

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 with potential in a range of solid tumors and blood 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 the optimal dose and regimen and identify a recommended Phase 2 dose for SY-1365, the ability to expand the ongoing Phase 1 clinical trial of SY-1365 into expansion cohorts, the role of CDK7 inhibition, and the benefits of Syros' gene control platform. The words ''anticipate,'' ''believe,'' ''continue,'' ''could,'' ''estimate,'' ''expect,'' ''intend,'' ''may,'' ''plan,'' ''potential,'' ''predict,'' ''project,'' "aim," ''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 the SY-1365 program, 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; 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 June 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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