

April 2, 2019



Syros Presents New Preclinical Data on SY-1365 and SY-5609 at AACR Annual Meeting

Presentations Highlight Syros' Leadership in Selective CDK7 Inhibition as Potentially Transformative Targeted Approach for Difficult-to-Treat Cancers

Alterations in RB Pathway Predictive of Response to SY-1365 in Ovarian Cancer Models, Supporting Further Evaluation as Potential Biomarker

Selectivity, Potency and Anti-Tumor Activity of SY-5609, an Oral CDK7 Inhibitor, Supports Advancement into IND-Enabling Studies

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS), a leader in the development of medicines that control the expression of genes, today presented new preclinical data across its franchise of selective cyclin-dependent kinase 7 (CDK7) inhibitors at the American Association for Cancer Research (AACR) Annual Meeting in Atlanta. New data on SY-1365, a first-in-class selective CDK7 inhibitor currently in a Phase 1 clinical trial, suggest that RB pathway alterations are predictive of response in preclinical models of high-grade ovarian cancer (HGOC) and support the ongoing clinical investigation of SY-1365 in patient populations enriched for RB pathway alterations. New preclinical data on SY-5609, a selective oral CDK7 inhibitor, demonstrate broad anti-tumor activity in preclinical models of triple-negative breast cancer (TNBC) and ovarian cancer.

"The new data on SY-1365 and SY-5609 further demonstrate our leadership in selective CDK7 inhibition, which we believe represents a potentially transformative targeted approach for many difficult-to-treat cancers," said Eric R. Olson, Ph.D., Syros' Chief Scientific Officer. "The data highlight our ability to discover highly selective small molecule inhibitors of CDK7, a target that has been historically difficult to drug selectively, as well as to identify potential patient selection strategies to enable targeted and efficient clinical development. We remain focused on executing on the ongoing Phase 1 trial evaluating SY-1365 in select ovarian and breast cancer patient populations that we believe are most likely to respond. Meanwhile, we also continue to advance SY-5609, our highly selective and potent oral CDK7 inhibitor, toward a Phase 1 study. Together, we believe SY-1365 and SY-5609 could make for a powerful CDK7 franchise with the potential to provide a profound benefit for patients."

RB Alterations Predictive of Response to SY-1365 in Preclinical Models

Researchers from Syros evaluated tumor growth inhibition in a panel of HGOC patient derived xenograft (PDX) models, including both high-grade serous ovarian cancer (HGSOC) and clear cell ovarian cancer, to determine whether RB pathway alterations predict response to treatment with SY-1365. RB pathway alterations are present in 67 percent of HGSOC patients, according to The Cancer Genome Atlas analysis. In Syros' study, RB pathway alterations were prospectively defined per The Cancer Genome Atlas criteria – including

RB1 deletion or mutation, CDKN2A downregulation or deletion, CCNE1 amplification, CCND1 amplification, or CCND2 upregulation.

These data show that:

- Ninety percent (9 of 10) of the PDX models with RB pathway alterations responded to treatment with SY-1365.
- Forty percent (6 of 15) of the PDX models without prospectively defined RB alterations responded to treatment with SY-1365, suggesting the presence of other undetected RB pathway changes or alternative mechanisms, including transcriptional regulation, conferring sensitivity to SY-1365.

Overall, Syros believes these results support the ongoing development of SY-1365 in patient populations, including HGSOc and CDK4/6-inhibitor resistant hormone receptor-positive (HR+) breast cancer, that are enriched for RB pathway alterations, as well as the evaluation of these alterations as potential biomarkers of response to SY-1365.

Syros is currently conducting a Phase 1 clinical trial assessing the safety and efficacy of SY-1365 as a single agent and in combination with standard-of-care therapies in multiple ovarian and breast cancer patient populations. The trial includes cohorts evaluating SY-1365 as a single agent in patients with relapsed ovarian clear cell cancer; as a single agent in HGSOc patients who have had three or more prior lines of therapy; in combination with carboplatin in HGSOc patients who have had one or more prior lines of therapy; in combination with fulvestrant in HR+ breast cancer patients who are resistant to treatment with a CDK4/6 inhibitor; and as a single agent in patients with solid tumors accessible for biopsy. Syros expects to report initial clinical data from the dose expansion portion of the trial in the fourth quarter of 2019. Additional details about the trial can be found using the identifier NCT03134638 at www.clinicaltrials.gov.

SY-5609 Demonstrates Selectivity, Potency and Anti-Tumor Activity Preclinically

Researchers from Syros conducted a series of preclinical studies to characterize the *in vitro* and *in vivo* profile of SY-5609. The data show that SY-5609:

- Demonstrated 13,000- to 49,000-fold greater selectivity for CDK7 over other CDK family members, including CDK2, CDK9 and CDK12.
- Induced robust tumor growth inhibition effects and cell cycle arrest in TNBC and ovarian cancer cell lines at low nanomolar drug concentrations, with apoptosis demonstrated only in the TNBC and ovarian cancer models, but not in non-cancerous cells.
- Significantly impacted tumor growth *in vivo*, with complete regressions observed with SY-5609 as a monotherapy in multiple TNBC and ovarian cancer cell line xenograft models at doses below the maximum tolerated dose.
- Demonstrated substantial tumor growth inhibition in multiple TNBC and ovarian cancer PDX models, with minimum weight loss observed.
- Led to decreases in CDK7 downstream protein markers, including MCL1, in treated tumor tissue, confirming CDK7 inhibition *in vivo*.

Syros is currently advancing SY-5609 through investigational new drug application enabling studies, with a Phase 1 oncology trial expected to begin in early 2020.

The posters presented at AACR are now available on the Publications and Abstracts section of the Syros website at www.syros.com.

About Syros Pharmaceuticals

Syros is pioneering the understanding of the non-coding regulatory region of the genome to advance a new wave of medicines that control the expression of genes. Syros has built a proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA 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 monogenic diseases and is advancing a growing pipeline of gene control medicines. Syros' lead drug candidates are SY-1425, a selective RAR α agonist in a Phase 2 clinical trial for genomically defined subsets of patients with acute myeloid leukemia, and SY-1365, a selective CDK7 inhibitor in a Phase 1 clinical trial focused on patients with ovarian and breast cancers. Syros is also developing a deep preclinical and discovery pipeline, including SY-5609, an oral CDK7 inhibitor, as well as programs in immuno-oncology and sickle cell disease. 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 relevance of RB pathway alterations to predict response to SY-1365 in clinical trials and the ability to identify a biomarker of response to SY-1365; the importance of CDK7 inhibition to address difficult-to-treat cancers and Syros' ability to develop a powerful CDK7 franchise; Syros' ability to advance its clinical-stage programs, including the timing and quantity of clinical data to be reported from the expansion phase of the ongoing Phase 1 clinical trial of SY-1365; the ability to complete IND-enabling preclinical studies and begin clinical development of SY-5609; and the benefits of Syros' gene control platform and product development pipeline. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "hope," "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-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; successfully progress SY-5609 through IND-enabling preclinical and toxicology studies; 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, including its ability to perform under the collaboration agreement with Incyte; 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’ Annual Report on Form 10-K for the year ended December 31, 2018, 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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Source: Syros Pharmaceuticals