June 23, 2017

Syros Presents Data at EHA Supporting Potential of SY-1425, Its First-in-Class Selective RARα Agonist, in Genomically Defined AML and MDS Patients

Preclinical Data Demonstrate Synergistic Activity of SY-1425 with Standard-of-Care AML and MDS Therapies and Anti-CD38 Therapies, Strengthening Rationale for Ongoing and Future Clinical Investigation of SY-1425 as Both a Monotherapy and Combination Agent

Preclinical Data Elucidates Mechanism of Action of SY-1425

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 preclinical data on SY-1425, its first-in-class selective retinoic acid receptor alpha (RARα) agonist currently in a Phase 2 clinical trial in genomically defined subsets of patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), were presented at the European Hematology Association (EHA) 22nd Congress in Madrid.

“The data presented at EHA support our belief that SY-1425 may provide a meaningful clinical benefit as both a monotherapy and a combination therapy for defined subsets of AML and MDS patients and serve as the foundation for our rational combination strategy for SY-1425,” said Nancy Simonian, M.D., Chief Executive Officer of Syros. “We are committed to broadly exploring the potential of SY-1425 through our Phase 2 clinical trial, which explores the safety and efficacy of SY-1425 as a single agent and in combination with a standard-of-care therapy, as well as through future clinical investigation of SY-1425 in combination with other targeted agents, including anti-CD38 therapies. We look forward to sharing initial clinical data from the ongoing Phase 2 trial this fall.”

SY-1425 in Combination with Hypomethylating AML and MDS Therapies
Syros presented data showing that hypomethylating agents (HMAs) increase the activity of SY-1425 in *in vitro* and *in vivo* models of AML with high levels of *RARA* expression. HMAs including azacitidine, a therapy used as a standard-of-care in AML and MDS, prime the DNA for gene activation, thus enhancing SY-1425’s gene activation and differentiation properties. In patient-derived xenograft (PDX) models of AML with high *RARA* expression, SY-1425 in combination with azacitidine shows:

- Greater clearance of tumor cells in bone marrow and other tissues, compared to either azacitidine or SY-1425 alone.
- Greater duration of response, compared to either azacitidine or SY-1425 alone.

Based on these data, Syros expanded its ongoing Phase 2 clinical trial to include an arm

assessing the safety and efficacy of SY-1425 in combination with azacitidine in newly diagnosed AML patients 60 years or older who are not suitable candidates for standard chemotherapy and who are positive for the Company's biomarkers of high expression of the RARA-pathway associated genes *RARA* and *IRF8*. The treatment regimen for patients in the combination arm uses full doses of both agents and is consistent with the one identified in preclinical studies to maximize tumor suppression and tolerability.

SY-1425 Sensitizes *RARA*-High AML Cells to Anti-CD38 Therapeutic Antibody
Syros presented data demonstrating that SY-1425 induces the cell surface protein CD38 in AML cells from patient samples with high levels of *RARA* expression. By inducing CD38, SY-1425 sensitizes the cells to daratumumab, an anti-CD38 monoclonal antibody that targets CD38-positive tumor cells for immune cell-mediated killing. Daratumumab is approved to treat various multiple myeloma (MM) populations. The preclinical studies show SY-1425:

- Induces levels of CD38 expression in *RARA*-high AML cells comparable to those in MM cells that are known to be responsive to daratumumab; notably, AML cells do not normally express high levels of CD38.
- Triggers robust activation of natural killer cells when combined with daratumumab in *RARA*-high AML cells.
- Leads to robust immune cell-mediated tumor cell death in *RARA*-high AML cells when combined with daratumumab.
- Induces higher levels of CD38 expression *in vivo* than ATRA, a non-selective agonist of the retinoic acid receptor family.

Based on these data, Syros believes SY-1425 in combination with an anti-CD38 antibody represents a potentially promising immunotherapy approach for defined subsets of AML patients and plans to pursue clinical development of the combination in these patients.

Mechanism of Action of SY-1425
Syros presented data showing that SY-1425 regulates genes known to be associated with the proliferation of AML cells and normal myeloid differentiation. Using its proprietary gene control platform to analyze regulatory regions of the genome, Syros scientists identified changes in enhancer landscapes, gene expression and transcription factor distribution in AML cells treated with SY-1425. These changes show that SY-1425 pushes AML cells with high expression of the *RARA* and *IRF8* genes into a more differentiated state. *RARA* and *IRF8* code for transcription factors that work together to induce differentiation of blood and bone marrow cells and reduce proliferation of blast cells. The data show that:

- In AML cells with high *RARA* and *IRF8* expression, treatment with SY-1425 triggers a differentiation program in which a critical set of transcription factors bind to various sites on the genome to either activate or inactivate enhancers. In doing so, these transcription factors create an enhancer profile in *RARA*-high and *IRF8*-high AML cells that is similar to the enhancer profiles of normal differentiated cell types.
- In *RARA*-high and *IRF8*-high AML cells treated with SY-1425, enhancers that were downregulated are enriched for binding sites for JUN and FOS, which are transcription factors known to drive proliferation, and enhancers that were upregulated are enriched for binding sites for RARα and IRF8, which are transcription factors known to be critical

for differentiation.

The ongoing Phase 2 trial of SY-1425 is assessing the safety and efficacy of SY-1425 as both a monotherapy and in combination with azacitidine in subsets of AML and MDS patients who are positive for the Company's *RARA* and *IRF8* biomarkers. Additional details about the trial can be found using the identifier NCT02807558 at www.clinicaltrials.gov.

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 therapeutic benefit of SY-1425 as a single agent and in combination with other drugs; the future clinical development of SY-1425 in combination with targeted agents such as anti-CD38 therapies; the reporting of initial clinical data from the ongoing Phase 2 clinical trial of SY-1425 in the fall of 2017; 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, 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 March 31, 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.

View source version on businesswire.com:
http://www.businesswire.com/news/home/20170623005068/en/

Media Contact:
Syros Pharmaceuticals
Naomi Aoki, 617-283-4298
naoki@syros.com
or
Investor Contact:
Stern Investor Relations, Inc.
Hannah Deresiewicz, 212-362-1200
hannahd@sternir.com

Source: Syros Pharmaceuticals, Inc.