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Syros Presents New Insights on Mechanism of Action of SY-1425, Its First-in-Class Selective RARα Agonist, in Oral Plenary Session at AACR Hematologic Malignancies Conference

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 new preclinical data that further elucidates the mechanism of action of SY-1425, its oral 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). These data demonstrate that SY-1425 represses genes known to be associated with the proliferation of AML cells, while activating genes critical for driving normal cell differentiation. These data were highlighted in an oral presentation during a plenary session at the American Association for Cancer Research (AACR) Hematologic Malignancies: Translating Discoveries to Novel Therapies conference.

“These findings strengthen the mechanistic rationale for believing that SY-1425 may provide a meaningful clinical benefit for defined subsets of AML and MDS patients,” said Eric Olson, Ph.D., Chief Scientific Officer of Syros. “Through systematic analysis of the regulatory genome, we discovered that high expression of *RARA* pathway-associated genes was driving disease in subsets of AML and MDS patients by stopping cells from differentiating. We are now showing that SY-1425 alters key regions of the regulatory genome in *RARA*-high AML cells, making those regions similar to ones in differentiated cells. These data provide additional evidence of the promise of SY-1425 in these subsets of AML and MDS patients. These data further demonstrate the power of our platform to elucidate the regulatory genome and make medicines that control the expression of genes with the goal of treating diseases that have eluded other genomics-based approaches.”

Using its proprietary gene control platform to analyze the regulatory genomes of 66 AML patients’ tumor samples, Syros scientists identified changes in highly specialized non-coding regulatory regions of DNA, known as super-enhancers, in subsets of AML cells treated with SY-1425. Because super-enhancers bring together large amounts of transcription factors and other regulatory proteins to drive the expression of the set of genes most critical to a given cell, their analysis sheds light on the complex transcriptional regulatory circuits that control the expression of critical genes and determine cell function. The data showed that:

- Super-enhancers associated with the *RARA* and *IRF8* genes are predictive of response to treatment with SY-1425. *RARA* and *IRF8* code for transcription factors that work cooperatively to induce differentiation of blood and bone marrow cells and reduce

proliferation of blast cells.

- In AML cells with high *RARA* 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 created an enhancer profile in *RARA*-high AML cells that was similar to the enhancer profiles of differentiated cell types such as macrophages and monocyte-derived dendritic cells.
- In *RARA*-high AML cells treated with SY-1425, enhancers that were downregulated are enriched for binding sites for the transcription factors JUN and FOS, which are known to drive proliferation, and enhancers that were upregulated are enriched for binding sites for the transcription factors RARα and IRF8, which are known to be critical for differentiation.

The ongoing Phase 2 trial of SY-1425 prospectively selects AML and MDS patients using biomarkers for the *RARA* and *IRF8* super-enhancers. 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 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 clinical utility of SY-1425 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

biomarkers associated with the *RARA* super-enhancer; 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’ Annual Report on Form 10-K for the year ended December 31, 2016, 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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