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# Syros Pharmaceuticals Presents Data at ASH Annual Meeting Further Supporting Clinical Potential of Its First-in-Class Selective RAR $\alpha$ Agonist for Genomically Defined Subsets of AML and MDS Patients

*SY-1425 Induces Similar Biological Changes in Preclinical Models of a Novel AML Subset as It Does In APL, the Approved Indication in Japan, Supporting Syros' Clinical Development Strategy*

*Data Provide Support for Clinical Investigation of SY-1425 in Combination with Standard-of-Care AML and MDS Therapies*

*Company Reveals Pharmacodynamic Markers to Measure Early Signs of Biological Activity in Ongoing Phase 2 Clinical Trial*

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS) today announced that new preclinical data on SY-1425, its first-in-class selective retinoic acid receptor alpha (RAR $\alpha$ ) 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 58<sup>th</sup> American Society of Hematology (ASH) Annual Meeting and Exhibition in San Diego.

“The new data further support the clinical potential of SY-1425 both as a single agent and in combination for AML and MDS patients whose disease is driven by abnormally high expression of the *RARA* gene,” said Nancy Simonian, MD, Chief Executive Officer of Syros. “There have been few advances in the treatment of AML and MDS over the past 20 years, and there is a dire need for better therapies. Based on SY-1425’s well-established safety and efficacy in acute promyelocytic leukemia, a form of AML driven by a distinct alteration in the *RARA* gene, and our strong preclinical data, we believe SY-1425 represents a promising therapeutic approach for subsets of AML and MDS patients and are committed to exploring its potential in the ongoing clinical trial as quickly and efficiently as possible.”

## **SY-1425 in AML with High *RARA* Gene Expression and APL with a *RARA* Gene Fusion**

Syros presented data showing that SY-1425 induced profound transcriptional and epigenomic changes in *in vitro* studies of AML cells with high levels of *RARA* gene expression. The changes are similar to those seen in acute promyelocytic leukemia (APL) cells, which are driven by fusions of the *RARA* gene with other genes, treated with SY-1425. Notably, SY-1425 did not induce these changes in AML cells with low levels of *RARA* gene expression. The consistent biological responses in AML cells with high *RARA* gene expression and APL support the clinical potential of SY-1425 in defined subsets of AML and

MDS patients. SY-1425 is approved to treat relapsed or refractory APL in Japan as Amnolake<sup>®</sup> (tamibarotene).

The data highlight that in AML cells with high *RARA* gene expression, SY-1425 induced:

- Significant changes in the expression of genes also associated with the cellular response of APL to retinoic acid receptor (RAR) agonists as well as in genes associated with apoptosis (programmed cell death), based on an analysis of 2,775 gene sets.
- Increased expression of *CD11b*, a gene involved in myeloid cell differentiation that is also induced in APL cells treated with RAR agonists.

### **SY-1425 in Combination with Standard-of-Care and Investigational Agents**

Syros presented additional data showing that SY-1425 increased the anti-tumor activity of chemotherapy, hypomethylating and investigational targeted agents in *in vitro* and *in vivo* models of AML with high levels of *RARA* gene expression. In these preclinical studies, SY-1425 demonstrated:

- Synergistic activity with idarubicin and azacitidine, which are standard-of-care treatments for AML and MDS, as well as JQ1, which is a BRD4 inhibitor, in AML cells with high *RARA* gene expression.
- Greater tumor growth inhibition and duration of response when used in combination with azacitidine, compared to either azacitidine or SY-1425 alone, in a patient-derived xenograft model of AML with high *RARA* gene expression.

Based on these data, Syros plans to explore the potential of SY-1425 in combination with other agents in future clinical trials.

### **Clinical Pharmacodynamic Markers to Measure Biological Activity of SY-1425**

Syros revealed pharmacodynamic markers, including markers of cell differentiation, that are being used to measure the biological activity of SY-1425 in the ongoing Phase 2 clinical trial. Two of these, *DHRS3* and *CD38*, provide early indicators to assess whether SY-1425 is affecting the targeted biology in AML and MDS patients. In preclinical studies in AML cells with high *RARA* gene expression:

- *DHRS3* was the most strongly and rapidly induced gene in response to treatment with SY-1425, with 100-fold induction in six hours.
- *DHRS3* gene expression correlated with the anti-proliferative activity of SY-1425.
- Expression of *CD38*, a gene involved in cell differentiation, also significantly increased in response to treatment with SY-1425.

Using its gene control platform, Syros discovered subsets of AML and MDS patients whose tumors have a highly specialized regulatory region of non-coding DNA, known as a super-enhancer, associated with the *RARA* gene, which codes for the RAR $\alpha$  transcription factor. The super-enhancer is believed to lead to over-expression of the *RARA* gene, locking cells in an immature, undifferentiated and proliferative state. Syros further investigated this unique biology, showing that the *RARA* super-enhancer is predictive of response to treatment with SY-1425 in preclinical AML models. Treatment with SY-1425 in cancer cells with this super-

enhancer promotes differentiation of these cells. Syros in-licensed SY-1425 for development and commercialization in North America and Europe in cancer.

The ongoing Phase 2 clinical trial of SY-1425 is a biomarker-directed multi-center, open-label trial exploring safety and efficacy in relapsed or refractory AML and high-risk MDS patients, newly diagnosed AML patients 60 years of age or older who are not suitable candidates for standard chemotherapy and low-risk transfusion-dependent MDS patients with high levels of *RARA* gene expression. The primary endpoint is overall response rate for AML and high-risk MDS patients and red blood cell transfusion-independence rate for low-risk MDS patients. Other endpoints include assessment of pharmacodynamic markers, duration of response, safety and tolerability, and overall and progression-free survival. Additional details about the trial can be found using the identifier NCT02807558 at [www.clinicaltrials.gov](http://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 RAR $\alpha$  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 potential therapeutic benefits of treatment with SY-1425 as a single agent or in combination with other agents in genomically defined subsets of AML and MDS patients, as well as plans to conduct clinical trials of SY-1425 in combination with other agents. 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; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; 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 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 the company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, which is on file with the Securities and Exchange Commission; and risks described in other filings that the company 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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