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# Syros Pharmaceuticals Presents Data Demonstrating Significant Anti-Tumor Activity of its Lead Drug Candidates at 21st Congress of the European Hematology Association

*–SY-1425 Highlighted in Oral Presentation Showing Cancer Growth Inhibition and Prolonged Survival in Preclinical Model of Acute Myeloid Leukemia with a Novel Biomarker –*

*– SY-1365 Induces Complete Tumor Regression and Extends Survival in Preclinical Models of Acute Leukemia –*

*– Presentations Underscore Potential of Company's Gene Control Platform to Identify and Drug Disease-Driving Targets –*

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals today announced that SY-1425, its potent and selective retinoic acid receptor alpha (RARα) agonist, was observed to inhibit the growth of cancer cells and prolong survival in an *in vivo* model of acute myeloid leukemia (AML) with a novel *RARA* biomarker discovered by the Company. Syros also announced that SY-1365, its first-in-class potent and selective cyclin-dependent kinase 7 (CDK7) inhibitor, was observed to selectively kill acute leukemia cells over non-cancerous cells and induce complete tumor regression and a significant survival benefit in *in vivo* models of AML. These data are being presented this week at the 21st Congress of the European Hematology Association (EHA) in Copenhagen, Denmark.

"The presentations at EHA highlight the potential of our gene control platform to systematically analyze the non-coding, regulatory region of the genome to advance a new wave of medicines designed to control the expression of disease-causing genes," said Nancy Simonian, MD, Chief Executive Officer of Syros. "By pioneering the understanding of this previously unexploited region of the genome, we believe we can identify novel disease drivers in specific patient populations and develop drugs that influence multiple disease-driving genes to provide patients with a more profound and durable benefit than many of today's targeted therapies. Based on these strong preclinical data, we are currently advancing SY-1425 into a Phase 2 trial in genomically defined subsets of relapsed or refractory AML and relapsed high-risk MDS patients and plan to advance SY-1365 into a clinical trial for acute leukemia in the first half of 2017."

**SY-1425 for Novel Genomically Defined Subsets of AML and MDS Patients**
The data on SY-1425, which will be detailed in an oral presentation Sunday at EHA, shows that a biomarker for a highly specialized regulatory region of non-coding DNA, known as a super-enhancer, that is associated with the RARA gene is predictive of response to

treatment with SY-1425 in AML cell lines and a patient-derived xenograft (PDX) model of AML. Treatment with SY-1425 was observed to inhibit cancer growth and prolong survival in a PDX model of AML with the *RARA* biomarker but not in a model of AML without the biomarker. Syros found the biomarker in approximately 25 percent of AML and myelodysplastic syndrome (MDS) patient tissue samples analyzed. Highlights of the data include:

- Greatly reduced tumor burden in the blood, bone marrow and spleen in a PDX mouse model with the *RARA* biomarker treated with SY-1425 compared to untreated mice; by contrast, no effect was seen in a PDX model of AML without the biomarker.
- Prolonged survival with 100 percent of mice with the *RARA* biomarker treated with SY-1425 alive at the end of the 35-day study; by contrast, none of the untreated mice survived beyond 25 days; notably, no survival benefit was seen in a PDX model of AML without the biomarker.
- No anti-tumor or survival benefit seen with ATRA, a less potent and non-selective retinoid, in a PDX model with the *RARA* biomarker.
- Differentiation of AML cells with the *RARA* biomarker treated with SY-1425.

Using its gene control platform, Syros identified subsets of AML and MDS patients whose tumors have the *RARA* super-enhancer. The super-enhancer is believed to lead to over-production of the RARα transcription factor, locking cells in an immature, undifferentiated and proliferative state. Treatment with SY-1425 inhibits cancer growth by promoting differentiation of AML cells with the *RARA* super-enhancer. Syros is on track to initiate a Phase 2 clinical trial of SY-1425 in mid-2016 in subsets of relapsed or refractory AML and relapsed high-risk MDS patients with the *RARA* biomarker.

**CDK7 Inhibition as a Novel Treatment Strategy for Acute Leukemia**
In the preclinical studies being presented Saturday at EHA, SY-1365 was observed to preferentially kill AML and acute lymphoblastic leukemia (ALL) cells over non-cancerous cells and induce tumor regression and significantly prolong survival in models of AML. Highlights of the *in vitro* and *in vivo* data include:

- Complete tumor regression, which was maintained through the end of the 38-day study, in 100 percent of treated mice in a cell-line derived xenograft model of AML.
- Strong survival benefit, with treated mice surviving up to 7-1/2 weeks beyond untreated mice in a PDX model of treatment-resistant AML.
- Robust, sustained and dose-dependent apoptosis in AML and ALL cells treated with SY-1365 while not inducing apoptosis in non-cancerous cells.
- Potent and selective inhibition of CDK7, with only six other kinases exhibiting greater than 90 percent binding when profiled across a panel of 468 kinases at a concentration of 1μM; notably, SY-1365 was not observed to significantly bind to members of the CDK family involved in cell cycle.
- Minimal effect on blood cell counts, including white blood cells, lymphocytes, neutrophils and reticulocytes, in an *in vivo* model, demonstrating a more favorable profile than a non-selective CDK inhibitor.
- Reduced expression of cancer-contributing genes associated with super-enhancers, including oncogenic transcription factors *MYB* and *MYC*, in an AML cell line.
- Synergistic activity when combined with other targeted agents in AML, including Flt3, Bcl-2 and pan-Brd inhibitors.

Certain cancers, including AML and ALL, are dependent on high and constant expression of transcription factors for their growth and survival and have been shown to be particularly responsive to selective inhibition of CDK7. Syros has generated several selective CDK7 inhibitors, which have been observed to delay tumor progression in *in vivo* models of additional transcriptionally addicted cancers, including *MYCN*-amplified neuroblastoma, small cell lung cancer and triple negative breast cancer. Syros selected SY-1365 as its development candidate based on its strong preclinical efficacy and safety and plans to begin a Phase 1/2 clinical trial of SY-1365 in acute leukemia in the first half of 2017.

**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, the Company's gene control platform has broad potential to achieve profound and durable benefit across a range of diseases. Syros is focused on cancer and immune-mediated diseases and is advancing a growing pipeline, including its lead drug candidates SY-1425, a selective RARα agonist for genomically defined subsets of patients identified by its platform, for a range of cancers including acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective CDK7 inhibitor for a range of blood cancers and solid tumors. Led by a team with deep experience in drug discovery, development and commercialization, Syros is located in Cambridge, Mass.

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