



Syros Presents PK and PD Data at ESMO for SY-1425, Its First-in-Class Selective RAR α Agonist, in Genomically Defined AML and MDS Patients

Data from Ongoing Phase 2 Clinical Trial Shows Favorable PK and Evidence of RAR α Target Engagement in Patients with Proprietary RARA or IRF8 Biomarkers

Company Expects to Present Initial Phase 2 Clinical Data for SY-1425 in Fourth Quarter of 2017

Company Also Details SY-1365 Phase 1 Clinical Trial Design

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 that pharmacokinetic (PK) and pharmacodynamic (PD) data from the ongoing Phase 2 clinical trial of SY-1425, its first-in-class selective retinoic acid receptor alpha (RAR α) agonist, in genomically defined subsets of patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), were presented at the European Society of Medical Oncology (ESMO) 2017 Congress in Madrid. Syros also presented the design of its ongoing Phase 1 clinical trial for SY-1365, a first-in-class selective cyclin-dependent kinase 7 (CDK7) inhibitor, in patients with advanced solid tumors.

"The PK and PD data we have seen to date from the ongoing Phase 2 clinical trial show that the dosing regimen of SY-1425 is achieving the intended drug exposure and eliciting a robust PD response with evidence of RAR α target engagement," said David A. Roth, M.D., Chief Medical Officer of Syros. "Importantly, SY-1425 showed favorable PK with continuous daily dosing, in contrast to historical experience with ATRA, a non-selective retinoic acid receptor agonist."

PK and PD Data from Ongoing Phase 2 Clinical Trial of SY-1425

Syros presented data based on an evaluation of 45 AML and MDS patients from the Company's ongoing Phase 2 clinical trial, including 36 patients evaluable for PK and 39 patients evaluable for PD. The data demonstrated that the dosing regimen being used in the clinical trial achieves blood levels sufficient to elicit a PD response with evidence of RAR α target engagement in patients who are positive for either the Company's *RARA* or *IRF8* biomarkers, or both. The data showed:

- Drug exposures consistent with those seen in patients with acute promyelocytic leukemia (APL). SY-1425 is approved to treat relapsed or refractory APL in Japan as

Amnolake[®] (tamibarotene) and has a well-established safety and efficacy profile in APL. The dosing regimen being used in the Phase 2 trial in *RARA* or *IRF8* biomarker-positive AML and MDS patients is the same as the dose approved in Japan for APL.

- No significant accumulation or reduction in SY-1425 exposure after two weeks of continuous dosing, demonstrating favorable PK properties in comparison to historical data with ATRA.
- Evidence of *RARα* target engagement, as measured by robust and sustained induction of *DHRS3* in the majority of patients evaluated. In preclinical studies, *DHRS3* was one of the most strongly induced genes in response to treatment with SY-1425, leading to the identification of *DHRS3* induction as a PD marker for use in the trial as an early indicator of whether SY-1425 is affecting the targeted biology.
- Similar induction of *DHRS3* across patients with relapsed or refractory AML, relapsed or refractory higher-risk MDS and lower-risk transfusion-dependent MDS.
- Similar induction of *DHRS3* across patients positive for either the *RARA* or *IRF8* biomarkers, or both.
- *Ex vivo* myeloid differentiation in a patient blood sample, confirming downstream functional impact of target engagement, including dose-dependent induction of *CD38*, a marker of cell maturation.

The Phase 2 clinical trial is assessing the safety and efficacy of SY-1425 as a monotherapy in four AML and MDS patient populations, as well as in combination with azacitidine, a standard-of-care therapy, in newly diagnosed AML patients who are not suitable candidates for standard chemotherapy. All patients enrolled in the trial are prospectively selected using the Company's *RARA* or *IRF8* biomarkers. Additional details about the trial can be found using the identifier NCT02807558 at www.clinicaltrials.gov. Syros remains on track to present initial clinical data from the trial in the fourth quarter of 2017.

Design of Ongoing Phase 1 Clinical Trial of SY-1365 in Advanced Solid Tumors

In a separate presentation, Syros detailed the design of its ongoing Phase 1 clinical trial of SY-1365 in patients with advanced solid tumors, including transcriptionally dependent cancers such as triple negative breast, small cell lung and ovarian cancers. The multi-center, open-label trial is expected to enroll approximately 70 patients. The primary objective of the trial is to assess the safety and tolerability of escalating doses of SY-1365, with the goal of establishing a maximum tolerated dose and a recommended Phase 2 dose (RP2D) and regimen. The dose-escalation phase is open to solid tumor patients for whom standard curative or palliative measures do not exist or are no longer effective. Following the dose-escalation phase, an expansion cohort is planned to further evaluate the safety and anti-tumor activity of SY-1365 in patients with triple negative breast, small cell lung and ovarian cancers, and to enroll patients with tumors of any histology in a cohort focused on analyzing biopsied tumor tissue. SY-1365 target engagement in peripheral blood mononuclear cells and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment. Additional details about the trial can be found using the identifier NCT03134638 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 RAR α 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 azacitidine; the reporting of initial clinical data from the ongoing Phase 2 clinical trial of SY-1425 in the fourth quarter of 2017; the ability to identify an appropriate dose and schedule to support expansion of the Phase 1 clinical trial of SY-1365, 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. Moreover, there can be no assurance that the PK and PD data generated to date in the ongoing Phase 2 clinical trial of SY-1425 are predictive of the ability of such trial to meet any of its endpoints. 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 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 June 30, 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.

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