Syros Publishes Foundational Data Supporting Ongoing Phase 2 Clinical Trial of SY-1425 for Genomically Defined AML and MDS Patients

Data Underscore Promise of Syros’ Gene Control Platform to Provide New Approach for Stratifying Patients with Potential to Lead to More Precise Diagnosis and Treatment

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS) today announced that data providing the foundation of its clinical development strategy for 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 published online in Cancer Discovery, a peer-reviewed journal of the American Association of Cancer Research. Syros is on track to present initial data from the Phase 2 clinical trial this fall.

The publication highlights Syros’ discovery of a subset of AML patients with a super-enhancer associated with the RARA gene, which was shown in preclinical studies to be predictive of response to SY-1425. Syros also found a subset of MDS patients with high expression of the RARA gene and demonstrated in ex vivo studies that RARA-high MDS had a similar response to SY-1425 as that seen in AML driven by the RARA super-enhancer.

“The publication of our work in Cancer Discovery is a demonstration of our pioneering approach for analyzing non-coding regulatory regions of the genome to identify disease-driving genes with the goal of developing new medicines that make a meaningful difference for patients,” said Eric Olson, Ph.D., Chief Scientific Officer of Syros. “Although genetic mutations associated with AML and MDS in protein-coding regions of the genome are well known, there are limited targeted therapy options in these diseases and there remains a high unmet need. Our investigation of the regulatory genome adds a new dimension to the understanding of AML and MDS disease biology that offers the potential to address these underserved patient populations and improve their prognosis and treatment.”

In collaboration with the Majeti lab at Stanford University School of Medicine, Syros used its gene control platform to analyze 66 AML patients’ tumor samples and identified six distinct patient subsets based on super-enhancer profiles, including one enriched for a super-enhancer associated with the RARA gene. The data show that:

- Super-enhancer profiles were strongly associated with survival outcomes, often independent of known genetic mutations in AML.
- The RARA super-enhancer was associated with high expression of the RARA gene, which codes for a transcription factor targeted by SY-1425.
- The RARA super-enhancer was predictive of response to SY-1425. In AML cells with high RARA expression, SY-1425 reduced proliferation and promoted differentiation. Moreover, SY-1425 decreased tumor burden and prolonged survival in patient-derived xenograft (PDX) models of AML with high RARA expression, while no effect was found on AML cells or PDX models with low RARA expression. Notably, ATRA, a less potent and non-selective retinoid, produced no survival benefit in PDX models with high RARA expression.
- SY-1425 induced profound transcriptional changes promoting cell differentiation in AML cells with high RARA expression but little to no transcriptional changes in AML cells with low RARA expression.
- DHRS3 was the most strongly and rapidly induced gene in response to treatment with SY-1425, leading to the identification of DHRS3 induction as a pharmacodynamic marker for use in the ongoing Phase 2 clinical trial as an early indicator of whether SY-1425 is affecting the targeted biology in defined subsets of AML and MDS patients.
- SY-1425 induced transcriptional and epigenomic changes in AML cells with high RARA expression similar to those seen in acute promyelocytic leukemia (APL) cells treated with SY-1425. SY-1425 is approved in Japan as Amnolake® (tamibarotene) to treat relapsed or refractory APL, a form of AML that is driven by fusions of the RARA gene, and has a well-established safety and efficacy profile in those patients.

The Phase 2 clinical trial of SY-1425 is assessing the safety and efficacy of SY-1425 as a single agent 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 in the trial are prospectively selected using biomarkers for high expression of RARA or IRF8, which are genes associated with the RARA pathway. 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 azacitidine; 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.


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