January 9, 2023

Syros Announces Clinical Updates and 2023 Strategic Priorities

-- Expect to Complete Enrollment in SELECT-MDS-1 Phase 3 Trial in 4Q 2023; Data Expected in 3Q 2024 --
-- On Track to Initiate Randomized Portion of SELECT-AML-1 Phase 2 Trial in 1Q 2023; Initial Data Expected 4Q 2023 --
-- Entering 2023 in Strong Financial Position, with Cash into 2Q 2025 --

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ:SYRS), a leader in advancing new standards of care for the frontline treatment of hematologic malignancies, today provided an update on its clinical development programs and outlined its strategic priorities for 2023.

“We are entering 2023 with a singular focus on developing and delivering new standards of care for the frontline treatment of hematologic malignancies,” said Nancy Simonian, M.D., Chief Executive Officer of Syros Pharmaceuticals. “We recently shared encouraging data from the safety lead-in portion of SELECT-AML-1, demonstrating that tamibarotene can combine with existing treatments with the goal of delivering better outcomes to newly diagnosed unfit AML patients positive for *RARA* gene overexpression, including those with a disease phenotype that may be resistant to venetoclax. These results support our advancement into the randomized portion of SELECT-AML-1, which we expect to initiate in the first quarter of 2023, and give us growing confidence in the potential for tamibarotene to provide clinical benefit to AML and MDS patients with *RARA* overexpression. We are on track to report initial data from this study in the fourth quarter of 2023.”

Dr. Simonian added, “In addition, we continue to open clinical sites and enroll newly diagnosed HR-MDS patients positive for *RARA* gene overexpression in our Phase 3 SELECT-MDS-1 trial. While we are encouraged by physician and patient enthusiasm at open clinical sites, we have experienced slower-than-anticipated site activations as we expanded the study global footprint and now expect data from the SELECT-MDS-1 trial in the third quarter of 2024.”

Program Updates and Upcoming Milestones

Tamibarotene: Higher-Risk Myelodysplastic Syndrome (HR-MDS)

Syros is evaluating tamibarotene in combination with azacitidine in newly diagnosed HR-MDS patients with *RARA* overexpression in the ongoing SELECT MDS-1 Phase 3 trial, which the company believes is the only Phase 3 trial currently recruiting in frontline HR-MDS. This randomized, double-blind, placebo-controlled study is intended to enroll 190 patients. Syros currently has over 75 clinical sites open for recruitment in 12 countries. Syros expects to complete patient enrollment in SELECT-MDS-1 in the fourth quarter of 2023, with data to follow in the third quarter of 2024.

Tamibarotene: Acute Myeloid Leukemia (AML)

Syros is evaluating tamibarotene in combination with venetoclax and azacitidine in newly diagnosed unfit AML patients with *RARA* overexpression. At the 64th American Society of Hematology (ASH) Annual Meeting in December 2022, Syros presented data from six response-evaluable patients from the safety lead-in portion of the ongoing SELECT-AML-1 Phase 2 trial, in which treatment with the triplet combination of tamibarotene, venetoclax and azacitidine demonstrated an 83 percent composite complete response rate and rapid onset of action, with no evidence of increased toxicity relative to historical data of the venetoclax and azacitidine doublet combination. Based on these data, Syros plans to initiate the randomized portion of the SELECT-AML-1 Phase 2 trial in the first quarter of 2023, directly comparing the triplet of tamibarotene, venetoclax and azacitidine to the doublet of venetoclax and azacitidine with initial randomized data expected in the fourth quarter of 2023 and additional data in 2024.

SY-2101: Acute Promyelocytic Leukemia (APL)

Syros is developing SY-2101, a novel oral form of arsenic trioxide (ATO) for the treatment of newly diagnosed APL patients. In August 2022, Syros reported promising preliminary data from its dose confirmation study of SY-2101, which showed that SY-2101 administered at 15 mg achieved comparable pharmacokinetic (AUC and Cmax) exposures to the approved intravenous (IV) dose of ATO administered at 0.15 mg/kg, with high oral bioavailability of approximately 80 percent and a favorable tolerability profile. Syros is encouraged by this initial data and, if additional data are supportive, intends to leverage these results to explore an alternative, more efficient registration strategy for SY-2101. Syros plans to provide an update on the dose confirmation study, as well as the development path and timing for further evaluation of SY-2101 in a registration enabling study in APL, in the second half of 2023.

CDK Inhibitor Portfolio and Discovery-Stage Oncology Programs

In November 2022, Syros announced initial data from the safety lead-in portion of its Phase 1 trial evaluating SY-5609 in combination with chemotherapy in patients with relapsed/refractory metastatic pancreatic cancer as well as an update from the single agent portion in advanced solid tumor patients. The data demonstrated encouraging safety and clinical activity in pancreatic cancer patients, including a partial response and an emerging exposure response relationship. Syros is continuing dose escalation of SY-5609 as a single agent and as a doublet with gemcitabine while seeking partnership opportunities for the program.

In addition, Roche continues to enroll patients in the arm of its ongoing Phase 1/1b INTRINSIC trial evaluating SY-5609 in combination with atezolizumab, its PD-L1 inhibitor, in BRAF-mutant colorectal cancer patients. Under the terms of the collaboration, Roche is the sponsor of the trial and Syros is supplying SY-5609.

As previously disclosed, Syros is also exploring partnership opportunities for its oncology discovery programs.

Financial Guidance

Based on its current operating plans, including the deferral of the SY-2101 registration enabling study, Syros expects that its existing cash, cash equivalents, and marketable securities will be sufficient to fund its anticipated operating expenses and capital expenditure requirements into the second quarter of 2025, beyond the Phase 3 data from the SELECT-MDS-1 trial and the initial data from the randomized portion of SELECT-AML-1 trial.

About Syros Pharmaceuticals

Syros is committed to developing new standards of care for the frontline treatment of patients with hematologic malignancies. Driven by the motivation to help patients with blood disorders that have largely eluded other targeted approaches, Syros is advancing a robust late-stage clinical pipeline, including tamibarotene, a first-in-class oral selective RARα agonist in patients with higher-risk myelodysplastic syndrome and acute myeloid leukemia with *RARA* gene overexpression, and SY-2101, a novel oral form of arsenic trioxide in patients with acute promyelocytic leukemia. Syros is also seeking partnerships for SY-5609, a highly selective and potent CDK7 inhibitor in clinical development for the treatment of select solid tumors, and multiple preclinical programs in oncology and monogenic diseases. For more information, visit www.syros.com and follow us on Twitter (@SyrosPharma) and LinkedIn.

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 Syros' clinical development plans, including with respect to the progression of its clinical trials involving tamibarotene, SY-2101 and SY-5609, the timing and impact of opening clinical sites, enrolling study participants and reporting clinical data, the pathway to receiving regulatory approval for Syros's drug candidates, the ability to deliver benefit to patients, the intention to seek partnerships for Syros's SY-5609 and oncology discovery programs, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into the second quarter of 2025, The words "anticipate," "believe," "continue," "could," "estimate," "expect," "hope," "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 tamibarotene, 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; sustain the response rates and durability of response seen to date with its drug candidates; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; 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, 2021 and Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, each of 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. In addition, the extent to which the COVID-19 pandemic continues to impact Syros' workforce and its clinical trial operations activities, and the operations of the third parties on which Syros relies, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the pandemic, additional or modified government actions, and the actions that may be required to contain the virus or treat its impact. 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.

This press release contains hyperlinks to information that is not deemed to be incorporated by reference in this press release.

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