November 15, 2018

Syros Announces Dose Escalation Data from Phase 1 Trial of SY-1365 Demonstrating Proof-of-Mechanism at Tolerable Doses in Patients with Advanced Solid Tumors

Dose Selected for Ongoing Expansion Cohorts in Ovarian and Breast Cancers Supported by Tolerability Profile and Early Signs of Clinical Activity

Data Highlighted in Oral Plenary Session at EORTC-NCI-AACR Meeting

Management to Host Conference Call and Webcast at 4:00 PM ET Today

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS), a leader in the development of medicines that control the expression of genes, today announced that data from the dose escalation portion of its Phase 1 trial of SY-1365, its first-in-class selective cyclin-dependent kinase 7 (CDK7) inhibitor, demonstrated proof-of-mechanism at tolerable doses in patients with advanced solid tumors. These data, the first clinical data reported on a selective CDK7 inhibitor, were highlighted in an oral plenary session at the 30th EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium in Dublin.

“These initial data on SY-1365 are highly encouraging,” said Dejan Juric, M.D., Director of the Termeer Center for Targeted Therapies at Massachusetts General Hospital and a clinical investigator in the Phase 1 study of SY-1365. “Patient data from the SY-1365 dose escalation study confirm the unique mechanism-of-action of this agent and demonstrate an acceptable tolerability profile along with early signs of single-agent activity. These data, coupled with preclinical evidence showing robust anti-tumor activity in a range of relapsed and treatment-refractory cancer models, support the ongoing development of SY-1365 for patients who currently have few, if any, effective treatment options.”

“As the first clinical data ever reported on a selective CDK7 inhibitor, these results mark an important milestone for SY-1365 and for the field of CDK7 inhibition,” said David A. Roth, M.D., Syros’ Chief Medical Officer. “We believe CDK7 inhibition is a potentially transformative new approach for treating many cancers that have eluded effective treatment with existing approaches. Now that we have demonstrated proof-of-mechanism at tolerable doses, we are committed to thoroughly exploring the potential of CDK7 inhibition for currently underserved patients. We are working to rapidly enroll the expansion cohorts in our ongoing Phase 1 study, focused initially on ovarian and breast cancers, while building on our leadership by advancing our highly selective and potent oral CDK7 inhibitor, SY-5609, as our next development candidate.”

Dose Escalation Data

The dose escalation portion of the Phase 1 trial characterized the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of SY-1365 in patients with advanced solid tumors to establish a dose and regimen for the expansion portion of the trial. PD assays used to establish proof-of-mechanism included a CDK7 occupancy assay to evaluate SY-1365 binding and a custom gene expression assay to evaluate downstream transcriptional changes in patients. Preliminary anti-tumor activity was also assessed.

Enrollment in the dose escalation portion of the trial was completed in September. In total, 32 patients were treated with SY-1365 as a single agent at doses ranging from 2 mg/m^2 to 112 mg/m^2 using either a weekly or twice weekly dosing regimen. Patients were treated for three weeks out of each four-week cycle. Patients had a range of solid tumors, the most prevalent being ovarian cancer (eight patients), breast cancer (eight patients) and endometrial cancer (five patients). Patients' median age was 63 (ranging from 25 to 87), with a median of five prior therapies (ranging from one to 13). As of an October 15th data snapshot, the median treatment duration was 46.5 days (ranging from two to 147 days) and four patients remained on treatment.

Safety

- Adverse events (AEs) were predominantly low-grade, reversible and generally manageable.
- The most commonly reported AEs were headache, nausea, vomiting and fatigue.
- No neutropenia was reported.
- Dose-limiting toxicities were headache, coronary vasospasm and fatigue.
- A maximum tolerated dose was not defined.

Pharmacokinetics

- Plasma PK exposures were linear over the doses tested.
- No drug accumulation was observed with repeat dosing.

Proof-of-Mechanism

- SY-1365 demonstrated dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells.
- At doses of 32 mg/m^2 and higher, CDK7 occupancy was greater than 50 percent when measured three days following dose administration, exceeding target occupancy levels in preclinical models that correlated with anti-tumor activity.
- CDK7 occupancy in blood cells was similar to target occupancy in tumor tissue biopsies available from two patients in the clinical trial.

Early Signs of Clinical Activity

As of the October 15th data snapshot, clinical activity per Response Evaluation Criteria in

Solid Tumors (RECIST) 1.1 criteria was observed in seven of the 19 patients (37%) who were evaluable for clinical responses, including:

- One patient with ovarian cancer in her fourth relapse who had a confirmed partial response (PR) after two cycles of treatment at the 80 mg/m^2 twice-weekly dose. The patient remained in PR at her CT assessment after six cycles and recently entered her seventh month on study treatment.
- Six additional patients who had stable disease, lasting between 50 and 127 days. Most of these patients received doses equal to or greater than 32 mg/m^2.

Based on these data, Syros selected a twice-weekly dose of 80 mg/m^2 of SY-1365 when administered as a single agent, and a once-weekly target dose of 80 mg/m^2 of SY-1365 when administered in combination with other agents, for further evaluation in the ongoing Phase 1 expansion cohorts in multiple ovarian and breast cancer patient populations.

Ongoing Expansion of Phase 1 Trial

Upon completing enrollment in the dose-escalation portion of the trial, Syros opened expansion cohorts to further assess the safety and anti-tumor activity of SY-1365 in multiple ovarian and breast cancer patient populations. The initial expansion strategy is based on preclinical data showing anti-tumor activity in these tumor types, a strong mechanistic rationale and high unmet need. The expansion cohorts are evaluating SY-1365: as a single agent in primary platinum-refractory ovarian cancer patients; as a single agent in ovarian cancer patients who have relapsed after three or more therapies; in combination with carboplatin in ovarian cancer patients who have relapsed after one or more prior therapies; and in combination with fulvestrant in patients with hormone-receptor positive (HR+) metastatic breast cancer who have progressed after treatment with a CDK4/6 inhibitor. An additional cohort is enrolling patients with any solid tumor accessible for biopsy to further evaluate the mechanism of action of SY-1365. Additional details about the trial can be found using the identifier NCT03134638 at www.clinicaltrials.gov.

The dose escalation data presented at the EORTC-NCI-AACR meeting is now available on the Publications and Abstracts section of the Syros website at www.syros.com.

Conference Call and Webcast

Syros will host a conference call today at 4:00 p.m. ET to discuss the data from the dose escalation portion of its Phase 1 trial.

The live call may be accessed by dialing (866) 595-4538 for domestic callers or (636) 812-6496 for international callers and referencing conference ID number: 4567679. A live webcast of the conference call will be available online on the Investors & Media section of the Syros website at www.syros.com. An archived replay of the webcast will be available for approximately 90 days.

About Syros Pharmaceuticals

Syros is pioneering the understanding of the non-coding regulatory region of the genome to advance a new wave of medicines that control the expression of genes. Syros has built a

proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA 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 monogenic 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 ovarian and breast cancers. Syros is also developing a deep preclinical and discovery pipeline, including SY-5609, an oral CDK7 inhibitor, as well as programs in immuno-oncology and sickle cell disease. 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 benefits of CDK7 inhibition and of SY-1365, alone or in combination with other therapeutic agents; the durability of clinical responses observed with SY-1365; the ability to enroll the expansion cohorts in the ongoing Phase 1 clinical trial and commence any future clinical studies of SY-1365; and the benefits of Syros' gene control platform. 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 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; 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, 2017, as updated in its Quarterly Reports on Form 10-Q for the quarters ended March 31, June 30 and September 30, 2018, 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. 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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Media Contact:

Naomi Aoki
Syros Pharmaceuticals
617-283-4298
naoki@syros.com

Investor Contact:
Hannah Deresiewicz
Stern Investor Relations, Inc.
212-362-1200
hannahd@sternir.com

Source: Syros Pharmaceuticals