May 29, 2020

Syros Presents New Preclinical Data on SY-5609 at 2020 ASCO Virtual Scientific Program

Highly Selective and Potent Oral CDK7 Inhibitor Shows Robust Anti-Tumor Activity in Colorectal Cancer Models

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today announced new preclinical data for SY-5609, its highly selective and potent oral inhibitor of cyclin-dependent kinase 7 (CDK7). The data show that SY-5609 inhibits tumor growth, including inducing sustained regressions, at well-tolerated doses in colorectal cancer models, supporting the inclusion of colorectal cancer patients in Syros' ongoing Phase 1 clinical trial. These data were presented as part of the 2020 American Society of Clinical Oncology Virtual Scientific Program (ASCO20).

"These data provide the first insights into the role of SY-5609 in driving anti-tumor activity in preclinical colorectal cancer models," said David A. Roth, M.D., Syros' Chief Medical Officer. "Two hallmarks of colorectal cancer are increased expression of cancer-driving transcription factors and activating mutations in oncogenes that drive cell cycle progression. By inhibiting CDK7, SY-5609 attacks both of these processes. These new data add to the substantial body of scientific evidence that CDK7 inhibition is a potentially transformative targeted approach for difficult-to-treat cancers. We are actively enrolling patients, including those with colorectal cancer, in our Phase 1 trial and look forward to reporting initial dose-escalation data in the fourth quarter of 2020."

New Preclinical Data Highlight Therapeutic Potential of SY-5609 in Colorectal Cancer
Syros scientists conducted a series of preclinical studies of SY-5609 in colorectal cancer cell lines, as well as in 30 independent patient-derived xenograft (PDX) models of colorectal cancer, including BRAF-mutant, KRAS-mutant and wild-type models. The data show that SY-5609:

- Potently inhibited proliferation and induced G2/M cell cycle arrest in KRAS- and BRAF-mutant colorectal cancer cell lines *in vitro*.
- Induced dose-dependent tumor growth inhibition, including complete regressions that were sustained after treatment discontinuation, with repeated daily dosing at well-tolerated doses that were associated with dose-dependent expression changes in cell cycle markers *E2F1* and *CCNB1* and the transcriptional marker *POLR2A* in a BRAF-mutant PDX model.
- Resulted in ≥ 50 percent tumor growth inhibition in 67 percent (20/30) of PDX models, and ≥ 90 percent tumor growth inhibition in 23 percent (7/30) of PDX models, including in models derived from heavily pre-treated patients, at well-tolerated doses.
    - Deeper responses, defined as ≥ 90 percent tumor growth inhibition, were

observed more frequently in models with BRAF mutations (50 percent, 5/10) relative to KRAS-mutant or wild-type models (10 percent, 1/10 each).
    - Regressions were seen in two BRAF-mutant models and one KRAS-mutant model.

Design of the Ongoing Phase 1 Clinical Trial of SY-5609
In a separate presentation at ASCO20, Syros detailed the design of its ongoing Phase 1 trial of SY-5609. The multi-center, open-label, Phase 1 trial is expected to enroll approximately 60 patients with advanced breast, colorectal, lung or ovarian cancer, or solid tumors of any histology that harbor Rb pathway alterations. The primary objectives of the dose escalation are to assess safety and tolerability of escalating doses of SY-5609, with the goal of establishing a maximum tolerated dose (MTD). Additional objectives include assessments of anti-tumor activity, pharmacokinetics (PK), pharmacodynamics (PD), and potential predictive biomarkers.

The trial is designed to move efficiently through dose escalation, initiating with a single-patient accelerated titration design before transitioning to a more traditional 3+3 dose escalation. To further characterize safety, PK and PD, and explore early signals of clinical activity, any dose level that has cleared the dose-limiting toxicity evaluation may be expanded to enroll up to 12 patients while dose escalation proceeds. Additionally, an amendment is planned to assess the safety of escalating doses of SY-5609 in combination with fulvestrant in HR-positive/HER2-negative metastatic breast cancer patients who have progressed after treatment with a CDK4/6 inhibitor.

Syros expects to report initial safety, tolerability, PK and PD data from the dose escalation in the fourth quarter of 2020. Additional dose-escalation data, including clinical activity data, are expected in mid-2021.

The posters are now available on the Publications and Abstracts section of the Syros website at www.syros.com.

About Syros Pharmaceuticals
Syros is redefining the power of small molecules to control the expression of genes. Based on its unique ability to elucidate regulatory regions of the genome, Syros aims to develop medicines that provide a profound benefit for patients with diseases that have eluded other genomics-based approaches. Syros is advancing a robust pipeline, including SY-1425, a first-in-class oral selective RARα agonist in a Phase 2 trial in a genomically defined subset of acute myeloid leukemia patients, and SY-5609, a highly selective and potent oral CDK7 inhibitor in a Phase 1 trial in patients with select solid tumors. Syros also has multiple preclinical and discovery 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 the timing for reporting data from the Phase 1 clinical trial of SY-5609, the ability to see signals of clinical activity in such trial, the future expansion of such trial including the initiation of a trial cohort evaluating SY-5609 in combination with fulvestrant, and the ability of SY-5609 to have a benefit for patients. 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 SY-5609 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 SY-5609; replicate scientific and non-clinical data in clinical trials; successfully establish a patient selection strategy and develop a companion diagnostic test to identify patients most likely to benefit from SY-5609; 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, 2019 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2020, 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 outbreak continues to impact our workforce and our research, supply chain and clinical trial operations activities, and the operations of the third parties on which we rely, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the outbreak, 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.

View source version on businesswire.com:
https://www.businesswire.com/news/home/20200529005047/en/

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

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

Source: Syros Pharmaceuticals