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Syros Presents New Data from Phase 1 Trial of SY-5609 and Details Three-Pronged Combination Strategy to Advance SY-5609 in Solid Tumors and Blood Cancer

Updated Dose-Escalation Data Demonstrate Clinical Activity in Heavily Pre-treated Patients Across Multiple Tumor Types

Plan to Initiate Expansion Evaluating SY-5609 in Combination with Chemotherapy in Pancreatic Cancer in 4Q 2021

Plan to Initiate Phase 1b Trial Evaluating SY-5609 in Combination with a BTK Inhibitor in Mantle Cell Lymphoma in 1H 2022

Evaluating SY-5609 in Combination with Immunotherapy in BRAF-Mutant Colorectal Cancer in Roche's Ongoing Phase 1/1b INTRINSIC Trial

Management to Host Conference Call at 4:00 p.m. 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 new data from the dose-escalation portion of the Phase 1 clinical trial of SY-5609, its highly selective and potent oral cyclin-dependent kinase 7 (CDK7) inhibitor, demonstrating clinical activity at tolerable doses as a single agent across multiple tumor types. The data is being presented today in an oral presentation at the 2021 ESMO Congress.

"I am encouraged by the results from this dose-escalation study," said Manish R. Sharma, M.D., Associate Director of Clinical Research at START Midwest in Grand Rapids, Michigan, and an investigator in the Phase 1 study of SY-5609. "This trial enrolled heavily pretreated patients with some of the most difficult-to-treat malignancies. Notably, the prolonged stable disease and tumor shrinkage seen in pancreatic cancer patients is distinct from what you would expect to see in this highly refractory patient population – particularly when treated with a single agent. Based on these results, together with preclinical data supporting combination strategies, I believe SY-5609 has the potential to provide a meaningful benefit for patients with cancers that have largely eluded treatment to date."

"The new data presented today demonstrate proof-of-activity for SY-5609 and point to an optimal dosing regimen with a tolerability profile that is amenable to multiple combination approaches," said David A. Roth, M.D., Chief Medical Officer of Syros. "As we move into this

next stage of development, we are introducing a three-pronged strategy to maximize the potential of SY-5609 and drive to proof-of-concept in combination with chemotherapy, a targeted therapy and an immunotherapy in both solid tumors and blood cancer. We believe this approach could unlock significant opportunities for SY-5609 and achieve the transformative potential of CDK7 inhibition for people with difficult-to-treat cancers.”

Dose-Escalation Data Demonstrate Clinical Activity Across Multiple Tumor Types

The Phase 1 multi-center, open-label dose-escalation study of SY-5609 enrolled patients with advanced breast, colorectal, lung, ovarian and pancreatic cancers, as well as patients with solid tumors of any histology harboring Rb pathway alterations. Patients were treated in cohorts exploring continuous daily dosing as well as intermittent dosing regimens, including seven days on treatment and seven days off (7d on/7d off) and five days on treatment and two days off (5d on/2d off).

As of July 6, 54 patients treated with single-agent SY-5609 in the study were eligible for a safety analysis and 45 patients were evaluable for clinical response. The median age of patients enrolled in the study was 65.5. Patients had been heavily pre-treated with as many as eight prior therapies and a median of four prior therapies.

Safety, Tolerability, Dose and Schedule

- Across all doses and schedules, the majority of adverse events (AEs) were low-grade and reversible. The most common treatment-emergent AEs were nausea, diarrhea, thrombocytopenia, fatigue and anemia.
- Low rate of discontinuations due to AEs.
- Tolerability was optimized with 7d on/7d off schedule, which had lowest rates of treatment-emergent AEs, while demonstrating comparable rates of stable disease (SD) as seen with more dose-intense regimens, supporting the selection of this schedule for further development of SY-5609.
- The maximum tolerated dose (MTD) of the 7d on/7d off schedule has not yet been reached.
- Changes in POLR2A mRNA expression, a pharmacodynamic (PD) marker for CDK7 inhibition, were associated with anti-tumor activity and were sustained for at least three days following drug cessation, supporting intermittent dosing.

Early Clinical Activity Data

- Thirteen patients (28.9%) achieved SD, with tumor regressions of up to 20% in six of those patients, across multiple tumor types.
- The most substantial clinical activity was observed in heavily pre-treated patients with advanced pancreatic cancer.
 - Five of 13 (38.5%) evaluable patients achieved SD, with tumor reductions in two of those patients.
 - Reductions in the CA 19-9 tumor marker, which is used in clinical practice to monitor tumor progression, were observed in three of four pancreatic cancer patients with serial CA 19-9 data. These reductions ranged from 32% to 72%.
 - Notably, one metastatic pancreatic cancer patient who had failed two prior lines of therapy and relapsed after a third line of treatment experienced prolonged SD of up to 10 months.
- Analysis of clinical activity by tumor type and mutational status supports the

mechanistic rationale for SY-5609 in Rb-altered and KRAS-mutant cancers.

Clinical Development Plans for SY-5609 in Solid Tumors and Blood Cancer

Further development of SY-5609 will explore three combination regimens, focusing initially on indications with compelling clinical and/or preclinical activity, as well as a strong mechanistic rationale and high unmet need.

Syros plans to initiate an expansion cohort evaluating SY-5609 in combination with chemotherapy for the treatment of pancreatic cancer in the fourth quarter of 2021. Syros also plans to initiate a Phase 1b trial evaluating SY-5609 in combination with a Bruton's tyrosine kinase (BTK) inhibitor for the treatment of mantle cell lymphoma in the first half of 2022. Syros plans to employ a 7d on/7d off dosing schedule in both of these trials. In addition, as announced in August 2021, Syros entered into an agreement with Roche to explore SY-5609 in combination with atezolizumab in patients with BRAF-mutant colorectal cancer in Roche's ongoing Phase 1/1b INTRINSIC trial.

New Preclinical Data Further Support Planned Expansion Strategy

Syros also presented new preclinical data at ESMO evaluating the anti-tumor and PD activity of intermittent dosing regimens for SY-5609, as well as new preclinical data evaluating SY-5609 as a single agent and in combination with chemotherapy in pancreatic cancer models. Taken together, these data further support Syros' dose expansion strategy, including the decision to use a 7d on/7d off dosing schedule and combine with chemotherapy in patients with pancreatic cancer. The data showed that SY-5609:

- Induced robust anti-tumor activity as a single agent in ovarian cancer models that was maintained at higher doses on intermittent schedules, including a 7d on/7d off schedule. *POLR2A* PD effects were sustained in tumor tissue through 72 hours post-dosing, consistent with what was observed in patients in the dose-escalation study.
- Induced regressions as a single agent in half (4/8) of the pancreatic cancer models that were studied, including models derived from heavily pre-treated patients.
- Resulted in deeper responses when combined on 7d on/7d off schedule with gemcitabine in KRAS-mutant pancreatic models than either agent alone.

Conference Call Information

Syros will host a conference call at 4:00 p.m. ET today to discuss these data, as well as the design of its dose expansion study. To access the live conference call, please dial 866-595-4538 (domestic) or 636-812-6496 (international), and refer to conference ID 4648345. A webcast of the call will also be available on the Investors & Media section of the Syros website at www.syros.com. An archived replay of the webcast will be available for approximately 30 days following the conference call.

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 clinical-stage pipeline, including: tamibarotene, a first-in-class oral selective RAR α agonist in RARA-positive patients with higher-risk myelodysplastic syndrome and acute myeloid leukemia; SY-2101, a novel oral form of arsenic trioxide in patients with acute promyelocytic leukemia; and SY-5609, a highly selective and potent oral CDK7 inhibitor in patients with select solid tumors and blood

cancers. Syros also has multiple preclinical and discovery programs in oncology and monogenic diseases.

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's clinical development plans and collaborations with respect to SY-5609, the anticipated timing to expand or initiate new clinical trials of SY-5609, the evaluation of SY-5609 in combination with other therapies, 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; sustain the response rates seen to date with 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, 2020 and Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, 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.

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