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Syros Announces First Patient Dosed in SELECT-AML-1 Trial of Tamibarotene in Combination with Venetoclax and Azacitidine in Newly Diagnosed Unfit AML

Initial Data from the Phase 2 Trial Expected in 2022

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today announced that the first patient has been dosed in the SELECT-AML-1 clinical trial of tamibarotene, its first-in-class selective retinoic acid receptor alpha (RARα) agonist, in combination with venetoclax and azacitidine. The randomized Phase 2 trial is enrolling RARA-positive newly diagnosed unfit patients with acute myeloid leukemia (AML).

“Despite recent advances, one third of newly diagnosed unfit AML patients still don’t respond to front-line treatment and many more relapse,” said Eytan M. Stein, M.D., Assistant Professor of Medicine and Director of the Program for Drug Development in Leukemia at Memorial Sloan Kettering Cancer Center. “These patients need new therapies that can deliver durable remissions with minimal or manageable toxicities. I am encouraged by tamibarotene’s distinct safety profile, as well as the compelling clinical and translational data that has emerged, suggesting it may benefit patients in the greatest need of new treatment options. I look forward to further exploring its potential in this clinical trial as part of a triplet regimen with venetoclax and azacitidine.”

Tamibarotene has demonstrated promising results in combination with azacitidine in RARA-positive newly diagnosed AML patients who are not suitable candidates for standard chemotherapy. At the 62nd American Society of Hematology (ASH) Annual Meeting in December 2020, Syros presented data from a Phase 2 clinical trial, demonstrating a 67% overall response rate and a 61% composite complete response (CR/CRi) rate. The data also showed that tamibarotene in combination with azacitidine was generally well-tolerated, with no evidence of increased myelosuppression compared to single-agent azacitidine.

Also at ASH, Syros presented translational data demonstrating that most RARA-positive newly diagnosed unfit AML patients in the Phase 2 trial of tamibarotene had a monocytic disease phenotype associated with resistance to venetoclax, which, in combination with azacitidine, is the standard of care for newly diagnosed unfit patients. These data suggest that the RARA biomarker selects for patients who are more likely to benefit from tamibarotene and who may be less likely to benefit from venetoclax.

“AML is a complex, heterogenous disease, and many patients may present upfront with both monocytic and non-monocytic leukemia cells,” said David A. Roth, M.D., Chief Medical Officer at Syros. “By employing a triplet strategy that combines tamibarotene with venetoclax

and azacitidine, we believe we can simultaneously target both cell types, reducing the emergence of resistant disease and increasing the likelihood of deeper and more durable responses. We are excited to be actively enrolling patients in this study, as we advance our portfolio of targeted hematology therapies with the aim of setting new standards of care for people with acute leukemias and myelodysplastic syndrome."

The SELECT-AML-1 trial is designed with a single-arm safety lead-in, followed by the randomized portion of the trial, which will evaluate the safety and efficacy of tamibarotene in combination with venetoclax and azacitidine compared to venetoclax and azacitidine in approximately 80 patients randomized 1:1. The trial will also evaluate the triplet regimen as a salvage strategy in patients in the control arm who do not respond to venetoclax and azacitidine. The primary endpoint of the trial will be composite CR rate.

Syros is also evaluating tamibarotene in combination with azacitidine in the SELECT-MDS-1 Phase 3 clinical trial in RARA-positive patients with newly diagnosed higher-risk myelodysplastic syndrome.

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 RARα 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. 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 Syros's clinical development plans, including with respect to tamibarotene, the timing of anticipated data readouts from the SELECT-AML-1 trial, and the ability of tamibarotene 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 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 tamibarotene; sustain the response rates and durability of response seen to date with tamibarotene; 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, 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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