December 12, 2022

Syros Pharmaceuticals Announces Publication in Blood Advances Demonstrating the Potential of Tamibarotene in Patients with RARA Gene Overexpression, Supporting Ongoing Clinical Development in AML and MDS

Combination of tamibarotene and azacitidine in a Phase 2 trial demonstrated a high complete response rate, with rapid onset and clinically meaningful durability in newly diagnosed unfit acute myeloid leukemia (AML) patients with RARA overexpression

Targeting RARA overexpression with tamibarotene is a novel targeted approach in newly diagnosed AML and MDS patients with potential to provide new frontline standards-of-care

Currently evaluating tamibarotene in Phase 3 SELECT-MDS-1 trial and Phase 2 SELECT-AML-1 trial; initial data from SELECT-AML-1 presented at 64th ASH Annual Meeting on December 10, 2022

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today announced a peer-reviewed publication of results from its completed biomarker-directed Phase 2 trial of tamibarotene in combination with azacitidine in newly diagnosed patients with acute myeloid leukemia (AML) who are not eligible for standard intensive chemotherapy. These findings support Syros' ongoing evaluation of tamibarotene for the treatment of AML and myelodysplastic syndrome (MDS) patients with *RARA* overexpression. The paper, titled "Targeting *RARA* Overexpression with Tamibarotene, a Potent and Selective RARα Agonist, is a Novel Approach in AML," was published online in *Blood Advances* on December 7, 2022 at https://doi.org/10.1182/bloodadvances.2022008806.

"We are excited to see a high CR rate and a rapid onset of response in newly diagnosed unfit AML patients with *RARA* overexpression treated with a combination of tamibarotene plus azacitidine. The biomarker test successfully identified AML patients positive for *RARA* overexpression who were enriched for response to tamibarotene and azacitidine relative to those patients who were negative for *RARA* overexpression. This observation further demonstrates that the activity of tamibarotene is dependent on the biology of *RARA* overexpression. In addition, the combination was generally well tolerated and provides the potential for a novel targeted treatment approach for patients with AML," said Stéphane de Botton, M.D., Head of Acute Myeloid Malignancies at Institut Gustave Roussy and a clinical investigator in the Phase 2 trial of tamibarotene.

“With approximately 30% of AML patients and 50% of HR-MDS patients positive for *RARA* overexpression, tamibarotene has the potential to contribute to a new frontline treatment paradigm for large, targeted patient populations,” said David A. Roth, M.D., Chief Medical Officer at Syros. “These data, including the high CR rate in patients with low blast count AML, informed our ongoing SELECT-MDS-1 Phase 3 trial in newly diagnosed HR-MDS patients and SELECT-AML-1 Phase 2 trial in newly diagnosed unfit AML patients, from which we reported encouraging data from the safety lead-in portion at the ASH Annual Meeting on December 10th.”

In the SY-1425-201 trial, a total of 51 patients at 12 sites in the U.S. and France were enrolled into the newly diagnosed unfit AML cohort that evaluated the combination of tamibarotene plus azacitidine. Patients were screened with a novel blood-based clinical trial assay used to prospectively identify those with *RARA* overexpression. Based on *RARA* expression levels, each patient was classified as positive for *RARA* overexpression (22 patients) or negative for *RARA* overexpression (29 patients). Both groups were enrolled and treated with 28-day treatment cycles, including azacitidine dosed daily on Days 1 to 7, followed by oral tamibarotene dosed twice daily on Days 8 to 28.

A total of 18 patients with *RARA* overexpression were response evaluable and exhibited an overall response rate (ORR) of 67% (12/18), CR/CRi rate of 61% (9 CR, 2 CRi), CR rate of 50% and morphological leukemia-free state of 5% (one patient). Median time to initial composite complete remission for patients with *RARA* overexpression was 1.2 months and median duration of composite complete remission was 10.8 months (95% CI: 2.9, NE). Importantly, in patients with low blast count AML, which is similar to HR-MDS, data showed a 67% (4/6) CR rate. In the patients without *RARA* overexpression, the response rates were consistent with treatment with azacitidine alone. Additionally, correlative analyses of *RARA* expression levels identified an association of *RARA* overexpression with a monocytic gene expression signature that may be associated with resistance to venetoclax. These data also informed the strategy of evaluating the triplet combination of tamibarotene, venetoclax and azacitidine in the ongoing SELECT-AML-1 trial.

Importantly, the tamibarotene plus azacitidine combination was generally well tolerated in the patients treated. The rates of myelosuppression were comparable to azacitidine monotherapy in this population suggesting no added hematologic toxicity from tamibarotene when used in combination with azacitidine. The majority of non-hematologic adverse events (AEs) were low grade.

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 patients with higher-risk myelodysplastic syndrome and acute myeloid leukemia with *RARA* gene overexpression; 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' clinical development plans, including with respect to the progression of its clinical trials involving tamibarotene and Syros' ability to deliver benefit to patients and develop new frontline standards-of-care. 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.

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Source: Syros Pharmaceuticals