December 10, 2022

Syros Presents Safety Lead-in Data from SELECT-AML-1 Trial Evaluating Tamibarotene in Combination with Venetoclax and Azacitidine and Announces Plans to Initiate Randomized Portion of Phase 2 Trial

– 83% composite complete response rate in newly diagnosed unfit AML patients with RARA gene overexpression –

- Initial safety and clinical activity profile of the triplet regimen supports advancing SELECT-AML-1 into the randomized portion–

– Management to host conference call at 12:00 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 data from the safety lead-in portion of its ongoing SELECT-AML-1 Phase 2 trial evaluating tamibarotene, an oral, selective retinoic acid receptor alpha (RARα) agonist, in combination with venetoclax and azacitidine in newly diagnosed, unfit patients with acute myeloid leukemia (AML) and *RARA* gene overexpression. The data is being presented today in a poster session at the 64th American Society of Hematology (ASH) Annual Meeting, taking place in New Orleans, LA.

“As a physician devoted to the care and treatment of leukemia, I am reminded daily of the limitations of existing therapeutic options, with approximately one-third of unfit AML patients failing to respond in the frontline setting and nearly all relapsing over time,” said Daniel Pollyea, M.D., M.S., Professor of Medicine and Clinical Director of Leukemia Services at the University of Colorado School of Medicine. “These data provide early evidence that tamibarotene can be combined with the existing standard-of-care to deliver improved outcomes to the approximately 30% of AML patients who are positive for *RARA* overexpression – many of whom present with a disease phenotype associated with features of venetoclax resistance. I look forward to enrolling patients in the randomized portion of the Phase 2 trial and to further characterizing the potential of tamibarotene as a novel combination agent for use in patients with hematologic malignancies.”

“We are highly encouraged by the initial data from SELECT-AML-1, which address the two questions we set out to answer in the safety lead-in, demonstrating both the tolerability of tamibarotene in combination with venetoclax and azacitidine, as well as the potential clinical benefit of adding tamibarotene to existing standard-of-care,” said David A. Roth, M.D., Chief

Medical Officer of Syros. “In AML patients with *RARA* gene overexpression, the triplet regimen with tamibarotene at full dose demonstrated a high response rate and rapid onset of action, with no evidence of increased toxicities beyond what would be expected with the combination of venetoclax and azacitidine. Based on these data, we intend to move rapidly to initiate the randomized portion of our Phase 2 SELECT-AML-1 trial, while also continuing to enroll patients in SELECT-MDS-1, where we are evaluating the combination of tamibarotene with standard-of-care azacitidine in patients with higher-risk myelodysplastic syndrome and *RARA* gene overexpression.”

Encouraging Initial Data from SELECT-AML-1 Phase 2 Trial
As of October 13, 2022, eight newly diagnosed, unfit, *RARA*-positive patients had been enrolled in the trial, including six who were evaluable for response. The median age of the patients was 61 (ranging from 55-82) and the median percent blasts at baseline was 63% (ranging from 39-100%).

Initial Safety Data
- Tamibarotene in combination with venetoclax and azacitidine administered at approved doses showed no evidence of increased toxicity relative to the doublet combination of venetoclax and azacitidine. This includes rates of myelosuppression, which were comparable to reports with venetoclax and azacitidine in this population.
- Serious adverse events (SAEs) were reported in all six patients. The most frequently occurring SAEs included febrile neutropenia (66%) and pneumonia (50%).
- The majority of non-hematologic AEs were low grade and reversible. The most frequently occurring non-hematologic AEs included pneumonia (66%), cough (50%), anxiety (50%), decreased appetite (50%) and rash (50%).

Initial Clinical Activity Data
- The complete response (CR) and complete response with incomplete blood count recovery (CRi) rate, as defined by Revised International Working Group (IWG) criteria was 83%, consisting of two patients (33%) who achieved a CR and three patients (50%) who achieved a CRi.
  ° Four of five patients (80%) who achieved a CR or CRi had a high monocytic expression score (MES), which may be associated with venetoclax resistance.[1]
- Median time to CR/CRi response was 33 days (ranging from 25-88).
- Median duration of treatment was 76.5 days (ranging from 20-104) and median duration of follow-up was 107 days (ranging from 56-314).
- These early data compare favorably to the standard-of-care combination of venetoclax and azacitidine, which shows composite CR rates of 66% in newly diagnosed unfit AML patients.[2]

Advancing Tamibarotene in Newly Diagnosed Unfit AML
Based on the encouraging data reported today, Syros plans to advance into the randomized portion of the SELECT-AML-1 Phase 2 trial, which will evaluate the safety and efficacy of tamibarotene in combination with venetoclax and azacitidine in approximately 80 patients positive for *RARA* overexpression randomized 1:1 to treatment with tamibarotene and venetoclax/azacitidine vs. venetoclax/azacitidine. The trial will incorporate venetoclax dose modification guidelines based on the recently published European LeukemiaNet (ELN) recommendations,[3] and will also evaluate the triplet regimen as a salvage therapy in patients who do not respond to venetoclax and azacitidine in the control arm. The

randomized portion is expected to initiate in Q1 2023, with data expected in 2023 or 2024.

The ASH presentation is now available on the Publications and Abstracts section of the Syros website at www.syros.com.

Conference Call Information

Syros will host a conference call at 12:00 p.m. ET today to discuss these data, as well as review the unmet need in newly diagnosed, unfit AML. In addition to Syros management, the event will feature a presentation from Daniel Pollyea, M.D., M.S., Associate Professor of Medicine, Clinical Director of Leukemia Services, University of Colorado School of Medicine. To access the live event, please register here. In addition, a live webcast of the presentation will 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 presentation.

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, the timing and impact of upcoming clinical data readouts, and Syros' ability to deliver benefit to 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 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.

This press release contains hyperlinks to information that is not deemed to be incorporated by reference in this press release.

[1] Fiore C, Kelly M, Volkert A, et al. Selection of RARA-positive Newly Diagnosed Unfit AML Patients with Elevated RARA Gene Expression Enriches for Features Associated with Primary Resistance to Venetoclax and Clinical Response to SY-1425, a Potent and Selective RARαAgonist, plus Azacitidine; ASH 2020 Abstract #137323.

[2] DiNardo CD, Jonas BA, Pullarkat MJ, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383:617-629. doi:10.1056/NEJMoa2012971.

[3] Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-77.

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