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Syros Announces Promising Clinical Data from Ongoing Phase 2 Trial of SY-1425 in Genomically Defined AML and MDS Patients at ASH Annual Meeting

SY-1425 in Combination with Azacitidine Shows 63% Overall Response Rate and Rapid Onset of Clinical Responses in RARA or IRF8 Biomarker-Positive Newly Diagnosed Unfit AML Patients

Initial Data from Biomarker-Positive and -Negative Azacitidine Combination Cohorts Support Potential Predictive Value of RARA and IRF8 Biomarkers for Patient Selection

SY-1425 Induced CD38 Expression in Majority of Patients in Daratumumab Combination Cohort in Relapsed/Refractory AML and Higher-Risk MDS Patients

Both Combinations Have Been Generally Well-Tolerated to Date

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS), a leader in the development of medicines that control the expression of genes, today announced initial clinical data from cohorts in its ongoing Phase 2 trial evaluating SY-1425, its first-in-class selective retinoic acid receptor alpha (RARα) agonist, in combination with azacitidine and with daratumumab in genomically defined patients with acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (MDS). These data are being presented at the 60th American Society of Hematology (ASH) Annual Meeting and Exposition.

“AML and MDS are complex diseases, and we need therapies that can be used in combination to help patients live longer and with a better quality of life,” said Rachel J. Cook, M.D., M.S., Assistant Professor of Medicine and Site Director for Acute Leukemia at the Knight Cancer Institute, Oregon Health and Science University and a clinical investigator in the Phase 2 study of SY-1425. “These data provide early clinical evidence that SY-1425 may be a meaningful treatment option for defined subsets of AML and MDS patients that is generally well-tolerated in combination with other therapies. I look forward to continuing to investigate SY-1425 to fully understand its potential to benefit patients.”

“These initial combination data from our ongoing Phase 2 trial of SY-1425 are promising,” said David A. Roth, M.D., Syros Chief Medical Officer. “SY-1425 in combination with azacitidine showed both a high response rate and rapid onset of clinical responses in AML patients selected with our *RARA* or *IRF8* biomarkers that we have not seen to date in the biomarker-negative cohort. The combination was generally well-tolerated with no evidence of increased toxicities beyond what would be expected with each agent alone, including myelosuppression that can sometimes be seen when combining drugs to treat leukemia. These data speak to the combination potential of SY-1425 as well as to the potential of our platform to identify patients most likely to respond to gene control medicines. We look forward to further characterizing the clinical activity of SY-1425 in combination with azacitidine as we continue to enroll and follow patients in the trial.”

SY-1425 in Combination with Azacitidine

The ongoing Phase 2 trial cohort is evaluating the safety and efficacy of SY-1425 in combination with azacitidine, a standard-of-care hypomethylating agent, in *RARA* or *IRF8* biomarker-positive patients with newly diagnosed AML who are not suitable candidates for standard chemotherapy. The trial also includes a cohort evaluating SY-1425 in combination with azacitidine in biomarker-negative newly diagnosed, unfit AML patients, with the aim of supporting the development of a commercial companion diagnostic. Patients in these cohorts were treated with azacitidine administered at standard daily doses of 75 mg/m^2 intravenously or subcutaneously for seven days, followed by SY-1425 administered at 6 mg/m^2 orally divided in two daily doses for the remainder of the 28-day cycle.

As of Oct. 29, 2018, 11 biomarker-positive and eight biomarker-negative patients had been enrolled in the trial. Of the biomarker-positive patients, 10 were evaluable for safety and eight were also evaluable for clinical responses. Of the biomarker-negative patients, seven were evaluable for safety and six were also evaluable for clinical responses. The median age of the biomarker-positive patients was 76 and the median age of the biomarker-negative patients

was 78, with more than half the patients in both cohorts having poor risk cytogenetics. Target enrollment in both the biomarker-positive cohort and the biomarker-negative cohort is 25, and Syros continues to enroll and follow patients.

Initial Safety Data

- SY-1425 in combination with azacitidine was generally well-tolerated with no evidence of increased toxicities.
- Adverse events (AEs) were consistent with what has been previously seen with SY-1425 or azacitidine as single agents in AML:
    - Across all grades and causalities, the most commonly reported AEs were decreased appetite (41%), fatigue (35%) and hypertriglyceridemia (35%).
    - The most commonly reported Grade 3 or higher AEs (all causality) were febrile neutropenia (24%), thrombocytopenia (24%), neutropenia (12%) and fatigue (12%).

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 50% in the biomarker-positive cohort.
- The overall response rate (ORR), using IWG criteria, was 63%, consisting of:
    - Three CRs, including one molecular CR.
    - One CRi.
    - One morphologic leukemia-free state (MLFS).
- Duration of these IWG responses ranged from 29 to 337 days, with four of the five responding patients remaining on treatment as of the data cutoff.
- Most of the initial responses were seen at the end of the first treatment cycle.
- These data compare favorably to single-agent azacitidine, which shows response rates of 18-29% in newly diagnosed unfit AML patients[1] with initial responses generally occurring after four cycles of treatment in most patients who respond[2].
- In the cohort of biomarker-negative patients, the ORR was 17%, with one of the six response-evaluable patients achieving a cytogenetic CR. While data from this cohort are less mature, the difference in the observed ORR supports the potential predictive value of the *RARA* and *IRF8* biomarkers for identifying patients most likely to respond to SY-1425.

SY-1425 in Combination with Daratumumab

The ongoing Phase 2 trial is characterizing CD38 induction with SY-1425 and evaluating the safety and efficacy of SY-1425 in combination with daratumumab in a pilot cohort of 12 *RARA* or *IRF8* biomarker-positive patients with relapsed or refractory AML or higher-risk MDS. Daratumumab is an anti-CD38 targeted therapy that is approved to treat multiple myeloma. While CD38 is normally expressed at high levels on multiple myeloma cells, AML cells have low CD38 expression. In preclinical studies, SY-1425 induced CD38 expression in AML cells, sensitizing them to treatment with daratumumab. Patients in this cohort were treated with SY-1425 as a single agent administered at 6 mg/m^2 orally, divided in two daily doses, for seven days, after which daratumumab was added and administered at 16 mg/kg intravenously weekly for eight doses, then biweekly for eight doses and every four weeks thereafter.

As of Oct. 29, 2018, nine patients had been enrolled in this cohort. All nine were evaluable for safety and CD38 induction, and six were also evaluable for clinical responses. The median age of these patients was 68, with more than half having poor risk cytogenetics. Syros continues to enroll patients to complete the pilot.

Initial Safety Data

- SY-1425 in combination with daratumumab was generally well-tolerated with no evidence of increased toxicities.
- AEs were consistent with what has been previously seen with single-agent SY-1425 in AML and MDS patients or single-agent daratumumab in multiple myeloma patients:
    - Across all grades and causalities, the most commonly reported AEs were febrile neutropenia (67%), anemia (44%), nausea (44%), vomiting (44%) and infusion-related reaction (44%).
    - The most commonly reported Grade 3 or higher AEs (all causality) were febrile neutropenia (67%) and anemia (44%).

Initial CD38 Induction and Clinical Activity Data

- Eight of the nine patients had increased CD38 expression in myeloid blast cells, with a median 1.57-fold induction as measured by mean fluorescence intensity (MFI), after seven days of treatment with SY-1425.
- CD38 expression increased in only two of these patients to levels exceeding those of a multiple myeloma cell line control:
  - One had an MLFS response.
  - The other progressed without a clinical response.

The initial clinical data on both combinations presented at the ASH meeting is now available on the Publications and Abstracts section of the Syros website at www.syros.com.

Additional details about the Phase 2 trial of SY-1425 can be found using the identifier NCT02807558 at www.clinicaltrials.gov.

About Syros Pharmaceuticals
Syros is pioneering the understanding of the non-coding regulatory region of the genome to advance a new wave of medicines that control the expression of genes. Syros has built a proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA to identify and drug novel targets linked to genomically defined patient populations. Because gene expression is fundamental to the function of all cells, Syros' gene control platform has broad potential to create medicines that achieve profound and durable benefit across a range of diseases. Syros is currently focused on cancer and monogenic diseases and is advancing a growing pipeline of gene control medicines. Syros' lead drug candidates are SY-1425, a selective RARα agonist in a Phase 2 clinical trial for genomically defined subsets of patients with acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective CDK7 inhibitor in a Phase 1 clinical trial for patients with ovarian and breast cancers. Syros is also developing a deep preclinical and discovery pipeline, including SY-5609, an oral CDK7 inhibitor, as well as programs in immuno-oncology and sickle cell disease. Led by a team with deep experience in drug discovery, development and commercialization, Syros is located in Cambridge, Mass.

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 potential benefits of SY-1425, including its ability to combine with other therapeutic agents; the potential predictive value of the RARA and IRF8 biomarkers; the ability to enroll the ongoing Phase 2 clinical trial of SY-1425 to completion; the ability to characterize the clinical activity of SY-1425; plans for further development of SY-1425 in combination with other therapies; and the benefits of Syros' gene control platform. 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. Moreover, there can be no assurance that the initial clinical data generated to date in the ongoing Phase 2 clinical trial of SY-1425 are predictive of the ability of either cohort of such trial to meet any of its endpoints or to continue comparing favorably with other treatments or treatment regimens. 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 SY-1425, 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; replicate scientific and non-clinical data in clinical trials; 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, 2017, as updated in its Quarterly Reports on Form 10-Q for the quarters ended March 31, June 30 and September 30, 2018, 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. 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.

[1] Prescribing Information, Celgene Revision 09/2018; Fenaux et al, JCO 2010; Dombret et al, Blood 2015
[2] Thepot et al, AJH 2014

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