UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): January 9, 2023

Syros Pharmaceuticals, Inc.
(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-37813**	**45-3772460**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

35 CambridgePark Drive **Cambridge, Massachusetts**	**02140**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 744-1340

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered or to be registered pursuant to Section 12(b) of the Act.

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, $0.001 par value	SYRS	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

From time to time, Syros Pharmaceuticals, Inc. (the "Company") intends to conduct meetings with third parties in which its current corporate slide presentation is presented. A copy of this slide presentation, dated January 2023, is furnished as Exhibit 99.1 to this Current Report on Form 8-K. The information responsive to Item 7.01 of this Form 8-K and Exhibit 99.1 hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On January 9, 2023, we issued a press release announcing our 2023 business objectives. The full text of this press release is filed as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference. The information contained on the websites referenced in the press release is not incorporated herein.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.	Description
99.1	Slide Presentation, dated January 2023
99.2	Press Release, dated January 9, 2023
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

SYROS PHARMACEUTICALS, INC.

Date: January 9, 2023

By: /s/ Jason Haas
Jason Haas
Chief Financial Officer

Exhibit 99.1

SYROS

Advancing Novel Treatments for Hematologic Malignancies

January 2023

Forward-looking statements

This presentation contains forward-looking statements (including within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and Section 27A of the Securities Act of 1933, as amended) concerning Syros and other matters, such as Syros' clinical development plans, including with respect to tamibarotene, SY-2101 and SY-5609, Syros' ability to deliver benefit to patients and value to stockholders, the timing and impact of upcoming clinical data readouts, the timing for submitting a new drug application to the Food and Drug Administration, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into 2Q 2025. These statements may discuss goals, intentions and expectations as to future plans, trends, events, results of operations or financial condition, or otherwise, based on management's current beliefs, as well as assumptions made by, and information currently available to, management. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as "may," "will," "should," "would," "expect," "anticipate," "plan," "likely," "believe," "estimate," "project," "intend," and other similar expressions. Statements that are not historical facts are forward-looking statements. Forward-looking statements are based on current beliefs and assumptions that are subject to risks and uncertainties and are not guarantees of future performance. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including, without limitation, Syros' ability to: advance the development of its programs, including tamibarotene, SY-2101 and 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 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. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors included in Syros' Annual Report on Form 10-K for the year ended December 31, 2021 and Syros' 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 (SEC). In addition, the extent to which the COVID-19 pandemic continues to impact our workforce and our discovery research, supply chain and clinical trial operations activities, and the operations of the third parties on which we rely, 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. Except as required by applicable law, Syros undertakes no obligation to revise or update any forward-looking statement, or to make any other forward-looking statements, whether as a result of new information, future events or otherwise.

Advancing new standards of care for the frontline treatment of hematologic malignancies

TARGETED HEMATOLOGY PORTFOLIO

Late-stage clinical trials in multiple hematology indications with the potential to set new standards of care, supported by a growing body of data

MULTIPLE NEAR-TERM CATALYSTS

Upcoming opportunities to build momentum and create value, including pivotal SELECT-MDS-1 data and randomized SELECT-AML-1 data

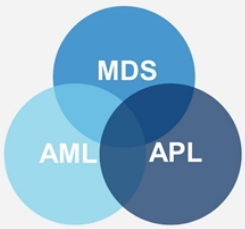
SIGNIFICANT MARKET OPPORTUNITIES IN FRONTLINE

Building infrastructure to target commercially synergistic patient populations that are underserved by existing options

STRONG CORPORATE POSITION

Cash runway to fund operations into 2Q 2025

3 clinical programs



Advancing our hematology focused late-stage clinical pipeline

Program	Indication	Early Clinical	Mid-clinical	Pivotal	Commercial Rights
Tamibarotene (oral RARα agonist)	Newly diagnosed HR-MDS (w/aza)	SELECT-MDS-1 Trial			SYROS Americas, Europe, Australia and Israel
	Newly diagnosed unfit AML (w/ven+aza)	SELECT-AML-1 Trial			
SY-2101 (oral ATO)	Newly diagnosed APL (w/ATRA)	PK and dose confirmation study			SYROS

Tamibarotene is approved in Japan as Amnolake® for patients with relapsed/refractory APL

Multiple value-driving milestones

Tamibarotene
in HR-MDS

Last patient enrolled from SELECT-MDS-1 Phase 3 trial	**4Q 23**
Pivotal data from SELECT-MDS-1 Phase 3 trial	**3Q 24**

Tamibarotene
in AML

Initiation of randomized SELECT-AML-1 trial	**1Q 23**
Initial data from randomized SELECT-AML-1 trial	**4Q 23**
Additional data from randomized SELECT-AML-1 trial	**2024**

SY-2101
in APL

Update on dose confirmation study, registration pathway and timing	**2H 23**

SYROS

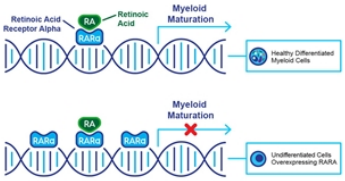
Tamibarotene

Opportunity to establish new SOC in MDS and AML patients with *RARA* overexpression

SYROS

Tamibarotene: Compelling profile that addresses large targeted populations

Tamibarotene is a **selective and potent** RARa agonist[1]



with tamibarotene

50% of patients with HR-MDS are positive for *RARA* overexpression[2]

RARA overexpression

30% of patients with AML are positive for *RARA* overexpression[3]

RARA overexpression

Competitive differentiation of tamibarotene

Biologically targeted[1]	✓
Oral	✓
High complete response rates[5,6]	✓
Rapid time to response[5,6]	✓
Favorable tolerability[4,5,6]	✓
Readily combinable[4,5,6]	✓
No additive myelosuppression[5,6]	✓

[1]McKeown, Cancer Discovery 2017;
[2]Patients with MDS: RARA-positivity based on Syros data on file from Study SY-1425-201 and the SELECT-MDS-1 Study (27May2022) from over 175 patients with MDS;
[3]Patients with AML: Prevalence of RARA-positive patients based on data presented at ESH 2017 and ESH 2019;
[4]Data presented at ASH 2017; [5]de Botton S., et al. Blood Advances 2022; [6]Data presented at ASH 2022

Significant unmet need in newly diagnosed HR-MDS

- Myelodysplastic syndrome (MDS) is a bone marrow disorder
- Higher-Risk MDS (HR-MDS) and acute myeloid leukemia (AML) are on a disease continuum; largely distinguished by % blasts in marrow[1,2,3]

"MDS-excess blasts" and "AML" essentially form a continuum…Rather than blast percentage, disease categorization may be more accurate if based on biologic features." *– Estey et al., 2022[3]*

~21,000 Newly Diagnosed HR-MDS patients in the US and EU annually[4]

MDS represents a **~$3.3B*** market by 2026

- HR-MDS is progressive in nature with a poor prognosis
  - Disease-related cytopenias result in significant morbidity and mortality with more than half of HR-MDS patients progressing to AML[5]
- Azacitidine, a hypomethylating agent (HMA), is SOC with a **17% CR rate** and a median OS of **18.6 months**[6]
  - **No new therapies** beyond HMAs approved since 2006[7]
- Elderly patient population seeking convenient, well tolerated therapies that can better control disease and maintain QOL

SYROS

[1]DiNardo CD, et al., Cancer. 2022; [2]Grob T, et al., Blood. 2022; [3]Elihu Estey, et al., Blood 2022; [4]Epidemiology projections from DRG Myelodysplastic Syndromes-Landscape & Forecast-Report 2020 and from DRG Acute Myelogenous Leukemia-Landscape & Forecast-Report 2020; NOTE*:Evaluate Pharma market estimate includes all risk groups for MDS; [5]Greenberg, Blood, 2012; [6]Garcia, J et al., Leukemia Research, 2021; [7]DeZern, AE. Hematology Am Soc Hematol Educ Program, 2015

Significant unmet need in newly diagnosed unfit AML

Acute myeloid leukemia is a cancer of the blood forming cells in the bone marrow
- ~50% of the patients are not eligible for intensive treatment and are considered “unfit”[1]

Precursor States → **MDS** → **HR-MDS** → **AML**

~25,000 Newly Diagnosed Unfit AML patients in US and EU annually[2]

Newly diagnosed AML represents a **~$6.6B*** market by 2025

- Venetoclax with azacitidine is SOC, with a **37%** CR rate and median OS of **14.7** months[3]
- Approximately **1/3** of patients do not respond, and nearly all relapse with a very poor prognosis, median OS of **2.4** months[4]

[1] Ferrara F., Clin Lymphoma Myeloma Leuk. 2011 [2]Epidemiology projections from DRG Acute Myelogenous Leukemia-Landscape & Forecast-Report 2020; NOTE*: market estimate includes all AML (fit and unfit); [3]DiNardo CD, et al., New England Journal of Medicine, 2020; [4]Maiti A., et al., Haematologica, 2021.

Encouraging, consistent data from multiple trials support clinical development strategy

Growing body of clinical evidence for tamibarotene in MDS and AML patients with *RARA* overexpression

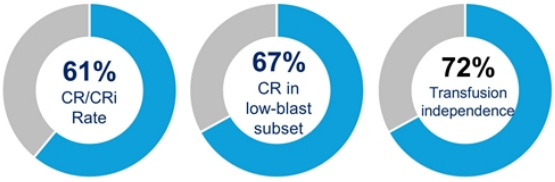
2017

Single-agent tamibarotene in R/R HR-MDS patients[1]

including one marrow CR

2020

Phase 2 data evaluating tami/aza in ND unfit AML patients[2]



Median time to response: **1.2 months**
Median duration of response: **10.8 months**
Overall survival for complete responders: **18 months**

2022

SELECT-AML-1 safety lead-in evaluating tami/ven/aza in ND unfit AML patients[3]

4/5 patients with CR/CRi had **high monocytic expression score (MES)** associated with venetoclax resistance

Median time to response: **1.1 months**

Tamibarotene in HR-MDS | Tamibarotene in AML

SYROS

[1]Data presented at ASH 2017; [2]de Botton S., et al. Blood Advances 2022; [3]Data presented at ASH 2022

Tamibarotene has a well-characterized and well-tolerated safety profile

Safety profile supports use of tamibarotene in combinations with azacitidine in MDS and with venetoclax/azacitidine in AML

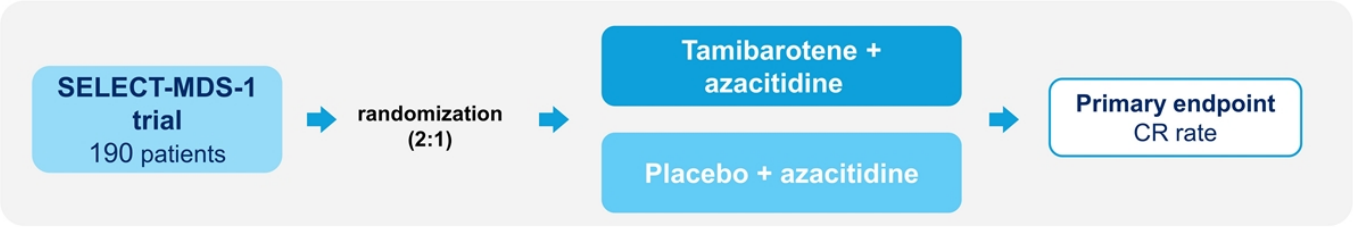
Over 1,000 APL patients treated with tamibarotene[1]	Single agent in AML and MDS patients and doublet (tami/aza) in AML patients[2,3]	Triplet (tami/ven/aza) in AML patients[4]

- Chronic daily dosing of tamibarotene as a single-agent and in combination with azacitidine has been generally well-tolerated.[2-4]
  - No evidence of increased toxicity in combination with rates of myelosuppression comparable to single-agent azacitidine.[2-4]
- As a triplet, myelosuppression is comparable to reports of venetoclax + azacitidine[4]
- The majority of non-hematologic AEs are low grade and reversible[1-4]

SYROS

[1]Amnolake® post-marketing surveillance data on file; [2]Data presented at ASH 2017; [3]de Botton S., et al. Blood Advances 2022; [4]Data presented at ASH 2022

Ongoing SELECT-MDS-1 Phase 3 trial in newly diagnosed HR-MDS patients with *RARA* overexpression

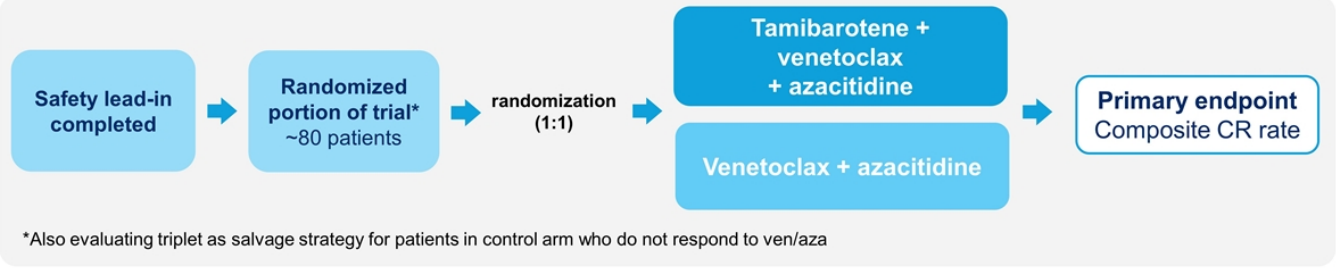


- Robustly designed, double-blind, placebo-controlled study
- 90% power to detect a difference in CR rates between experimental and control arms
- 2:1 randomization with one-sided alpha of 0.025
- FDA feedback supports:
  - Focus on population with *RARA* overexpression
  - CR as primary endpoint for approval
  - Azacitidine as appropriate comparator

Key Milestones

Last patient enrolled from SELECT-MDS-1 Phase 3 trial	**4Q 23**
Pivotal data from SELECT-MDS-1 Phase 3 trial	**3Q 24**

Ongoing SELECT-AML-1 Phase 2 trial of triplet regimen (tami/ven/aza) in ND unfit AML patients with *RARA* overexpression



*Also evaluating triplet as salvage strategy for patients in control arm who do not respond to ven/aza

Translational data support potential for *RARA* overexpression biomarker to enrich for patients more likely to respond to tamibarotene, for whom the standard of care is suboptimal

- 1/3 of patients do not respond to upfront treatment with ven/aza and a majority of those with initial response ultimately relapse
- Venetoclax resistance is associated with monocytic phenotype[1-3]; most patients with *RARA* overexpression, including those who achieved CR/CRi in tamibarotene trial, have a monocytic phenotype[4]

Key Milestones

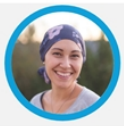
Initiation of randomized SELECT-AML-1 trial	**1Q 23**
Initial data from randomized SELECT-AML-1 trial	**4Q 23**
Additional data from randomized SELECT-AML-1 trial	**2024**

SYROS [1]Zhang, Nature 2018; [2]Kuusanmäki, Haematologica 2019; [3]Pei, Cancer Discovery 2020; [4]Fiore, ASH 2020

SY-2101

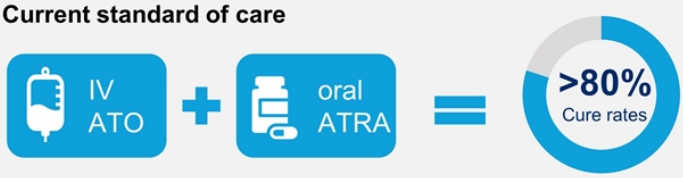
Highly synergistic with our hematology portfolio

Significant unmet need in newly diagnosed APL



Acute promyelocytic leukemia (APL) is a unique subtype of AML and is defined by a fusion of the *RARA* and *PML* genes.

Current standard of care



Treatment burden
Current typical course of treatment involves infusions up to **140 x 2-4 hrs** over **nearly a year**

Opportunity to reduce treatment burden, increase access and reduce health care costs

Market opportunity for an oral therapy

APL accounts for

~10% of all adult AML cases diagnosed in US and Europe annually

~2,000 patients are diagnosed with APL in the US and EU annually

SYROS

FS26 Acute Promyelocytic Leukemia Facts, 2015;
NCCN AML treatment guidelines (Nov 2020); Trisenox (arsenic trioxide) USPI

SY-2101 has the opportunity to become SOC in frontline APL

- Novel oral form of arsenic trioxide (ATO) with opportunity to replace standard of care for APL patients
- Orally bioavailable with exposures consistent with IV ATO
- Clear development path to approval in frontline APL with potential to leverage emerging data for a more efficient pivotal study
- Potential for rapid adoption in frontline APL, benefitting from a specialty commercial effort and synergies with tamibarotene

Clear development path to approval in frontline APL with potential to leverage emerging data for a more efficient pivotal study

Feedback from the FDA and EMA in the context of original SY-2101 PK data supports a single registration study of approximately 215 patients designed with mCR and EFS as primary endpoints for potential approval

Emerging PK cross-over data directly comparing SY-2101 to the approved dose of IV ATO are encouraging

- SY-2101 showed high oral bioavailability of ~80%
- Exposures of SY-2101 are comparable to IV ATO administered at 0.15 mg/kg based on both Cmax and AUC

Based on these emerging data, there may be an opportunity to explore a more efficient registration pathway to potential approval

Plan to provide a further update on dose confirmation data, regulatory pathway and timing in 2H 2023

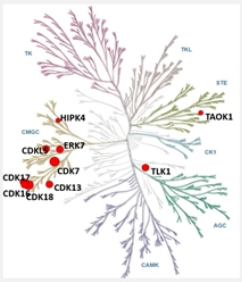
SY-5609

Highly selective and potent oral CDK7 inhibitor

SYROS

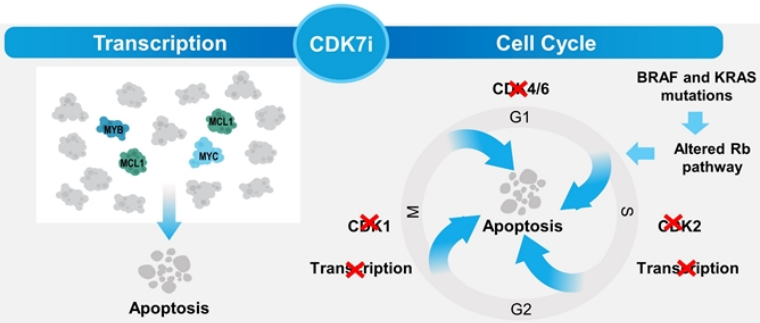
SY-5609: Highly selective and potent oral CDK7 inhibitor

- Phase 1 study in pancreatic cancer and select solid tumor patients demonstrates promising clinical activity
- Well-tolerated safety profile in combination with predominantly low-grade AEs
- Broad potential in multiple difficult-to-treat cancer populations, including PDAC and CRC



- 100-91% Inhibition
- 90-80% Inhibition
- 79-71% Inhibition

SY-5609 is highly selective with sub-nanomolar potency[1]



[1]Marineau JJ et al, 2021, Discovery of SY-5609: A Selective, Noncovalent Inhibitor of CDK7, J Med Chem
Data presented in October 2019 at EORTC-NCI-AACR Conference

Clinical activity including a confirmed PR and emerging exposure-response relationships in ongoing Phase 1 single agent and combination cohorts

Optimized Dosing Schedule: SY-5609 administered 7d on/7d off

Single Agent – Dose Escalation from 4 mg to 10 mg

Patient population
Relapsed/refractory patients with select solid tumors

Dose escalation to evaluate safety, tolerability, and signs of clinical activity

- Well tolerated safety profile; MTD has not been reached
- 30 patients dosed across five levels (4 to 10 mg), with only 1 DLT (4 mg dose level/grade 3 diarrhea)
- Clinical activity observed, including 2/2 response evaluable patients with SD at 10 mg, w/ 1 PDAC patient with 10% tumor reduction
- Emerging exposure-response relationship

Combination: SY-5609 starting at 4 mg w/gemcitabine +/- nab-paclitaxel*

*Gemcitabine and nab-paclitaxel administered at approved doses

Patient population
Metastatic patients who have progressed following treatment with FOLFIRINOX

Safety lead in cohorts to evaluate safety, tolerability, and signs of clinical activity

- Well tolerated safety profile; MTD has not been reached
- AE profile consistent with single agent SY-5609 or gemcitabine monotherapy or gemcitabine/nab-paclitaxel
- One patient with confirmed PR and 98% reduction CA-19-9 at the 4 mg 5609 dose level in combination with gemcitabine
- 50% (4/8) DCR in patients treated at 4 and 5 mg levels in combination with gemcitabine
- Emerging exposure-response relationship, with PR patient demonstrating higher-than-average exposure for the dose administered

Continued dose escalation of SY-5609 as a single agent and with gemcitabine while seeking partnership opportunities

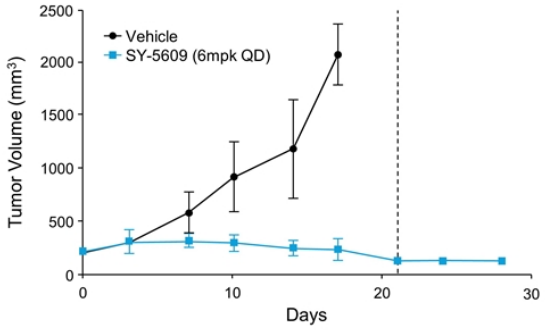
SYROS

Data as of October 2022

Preclinical data support SY-5609 in BRAF-mutant CRC in combination with PDL1 inhibitor: SY-5609 part of Roche's Phase 1/1b INTRINSIC trial

First clinical investigation of CDK7 inhibitor with an immunotherapy

Robust anti-tumor activity in BRAF-mutant CRC model as single agent



- 67% (20/30) of models demonstrated ≥ 50% tumor growth inhibition
- 23% (7/30) demonstrated deep responses of ≥ 90% tumor growth inhibition
- Deep responses enriched in BRAF-mutant (5/10) models

Key Milestones:

- Roche is actively enrolling patients in the arm of its ongoing Phase 1/1b INTRINISIC trial evaluating SY-5609 in combination with atezolizumab
  - Roche is the sponsor of the trial and Syros is supplying SY-5609

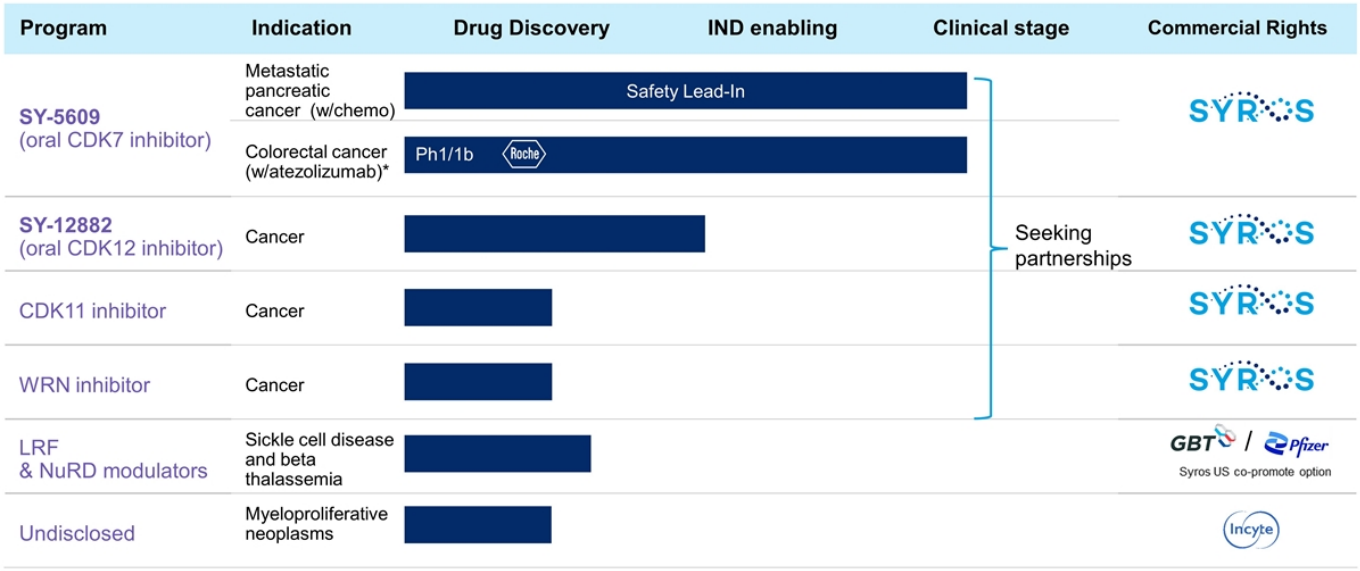
CDK7 inhibition enhances anti-tumor activity of PD-1 inhibition[1]

- CDK7 inhibitor induces DNA replication stress and genome instability in cancer cells, triggering immune-response signaling
- In animal models, CDK7 inhibitor enhances tumor response to anti-PD1 immunotherapy
  - Prolonging overall survival, and increasing immune cell infiltrates

CRC data presented in May 2020 at ASCO Virtual Symposium; [1]Zhang et al., Cancer Cell, 2020.

Earlier Stage Programs

Earlier stage programs



*Roche-sponsored trial

Rapidly advancing toward our vision

Now

Advancing late-stage targeted hematology pipeline

Preparing for product launch and commercialization

Seeking partnership opportunities for SY-5609 and discovery programs

Cash runway to fund planned operations into Q2 2025

Vision

Commercial company with medicines that provide a profound benefit for cancer patients

SYROS


SYROS

Exhibit 99.2

Syros Announces Clinical Updates and 2023 Strategic Priorities

— Expect to Complete Enrollment in SELECT-MDS-1 Phase 3 Trial in 4Q 2023; Data Expected in 3Q 2024 —
— On Track to Initiate Randomized Portion of SELECT-AML-1 Phase 2 Trial in 1Q 2023; Initial Data Expected 4Q 2023 —
— Entering 2023 in Strong Financial Position, with Cash into 2Q 2025 —

CAMBRIDGE, Mass., January 9, 2023 – Syros Pharmaceuticals (NASDAQ:SYRS), a leader in advancing new standards of care for the frontline treatment of hematologic malignancies, today provided an update on its clinical development programs and outlined its strategic priorities for 2023.

"We are entering 2023 with a singular focus on developing and delivering new standards of care for the frontline treatment of hematologic malignancies," said Nancy Simonian, M.D., Chief Executive Officer of Syros Pharmaceuticals. "We recently shared encouraging data from the safety lead-in portion of SELECT-AML-1, demonstrating that tamibarotene can combine with existing treatments with the goal of delivering better outcomes to newly diagnosed unfit AML patients positive for *RARA* gene overexpression, including those with a disease phenotype that may be resistant to venetoclax. These results support our advancement into the randomized portion of SELECT-AML-1, which we expect to initiate in the first quarter of 2023, and give us growing confidence in the potential for tamibarotene to provide clinical benefit to AML and MDS patients with *RARA* overexpression. We are on track to report initial data from this study in the fourth quarter of 2023."

Dr. Simonian added, "In addition, we continue to open clinical sites and enroll newly diagnosed HR-MDS patients positive for *RARA* gene overexpression in our Phase 3 SELECT-MDS-1 trial. While we are encouraged by physician and patient enthusiasm at open clinical sites, we have experienced slower-than-anticipated site activations as we expanded the study global footprint and now expect data from the SELECT-MDS-1 trial in the third quarter of 2024."

Program Updates and Upcoming Milestones

Tamibarotene: Higher-Risk Myelodysplastic Syndrome (HR-MDS)

Syros is evaluating tamibarotene in combination with azacitidine in newly diagnosed HR-MDS patients with *RARA* overexpression in the ongoing SELECT MDS-1 Phase 3 trial, which the company believes is the only Phase 3 trial currently recruiting in frontline HR-MDS. This randomized, double-blind, placebo-controlled study is intended to enroll 190 patients. Syros currently has over 75 clinical sites open for recruitment in 12 countries. Syros expects to complete patient enrollment in SELECT-MDS-1 in the fourth quarter of 2023, with data to follow in the third quarter of 2024.

Tamibarotene: Acute Myeloid Leukemia (AML)

Syros is evaluating tamibarotene in combination with venetoclax and azacitidine in newly diagnosed unfit AML patients with *RARA* overexpression. At the 64th American Society of Hematology (ASH) Annual Meeting in December 2022, Syros presented data from six response-evaluable patients from the safety lead-in portion of the ongoing SELECT-AML-1 Phase 2 trial, in which treatment with the triplet combination of tamibarotene, venetoclax and azacitidine demonstrated an 83 percent composite complete response rate and rapid onset of action, with no evidence of increased toxicity relative to historical data of the venetoclax and azacitidine doublet combination. Based on these data, Syros plans to initiate the randomized portion of the SELECT-AML-1 Phase 2 trial in the first quarter of 2023, directly comparing the triplet of tamibarotene, venetoclax and azacitidine to the doublet of venetoclax and azacitidine with initial randomized data expected in the fourth quarter of 2023 and additional data in 2024.

SY-2101: Acute Promyelocytic Leukemia (APL)

Syros is developing SY-2101, a novel oral form of arsenic trioxide (ATO) for the treatment of newly diagnosed APL patients. In August 2022, Syros reported promising preliminary data from its dose confirmation study of SY-2101, which showed that SY-2101 administered at 15 mg achieved comparable pharmacokinetic (AUC and Cmax) exposures to the approved intravenous (IV) dose of ATO administered at 0.15 mg/kg, with high oral bioavailability of approximately 80 percent and a favorable tolerability profile. Syros is encouraged by this initial data and, if additional data are supportive, intends to leverage these results to explore an alternative, more efficient registration strategy for SY-2101. Syros plans to provide an update on the dose confirmation study, as well as the development path and timing for further evaluation of SY-2101 in a registration enabling study in APL, in the second half of 2023.

CDK Inhibitor Portfolio and Discovery-Stage Oncology Programs

In November 2022, Syros announced initial data from the safety lead-in portion of its Phase 1 trial evaluating SY-5609 in combination with chemotherapy in patients with relapsed/refractory metastatic pancreatic cancer as well as an update from the single agent portion in advanced solid tumor patients. The data demonstrated encouraging safety and clinical activity in pancreatic cancer patients, including a partial response and an emerging exposure response relationship. Syros is continuing dose escalation of SY-5609 as a single agent and as a doublet with gemcitabine while seeking partnership opportunities for the program.

In addition, Roche continues to enroll patients in the arm of its ongoing Phase 1/1b INTRINSIC trial evaluating SY-5609 in combination with atezolizumab, its PD-L1 inhibitor, in BRAF-mutant colorectal cancer patients. Under the terms of the collaboration, Roche is the sponsor of the trial and Syros is supplying SY-5609.

As previously disclosed, Syros is also exploring partnership opportunities for its oncology discovery programs.

Financial Guidance

Based on its current operating plans, including the deferral of the SY-2101 registration enabling study, Syros expects that its existing cash, cash equivalents, and marketable securities will be sufficient to fund its anticipated operating expenses and capital expenditure requirements into the second quarter of 2025, beyond the Phase 3 data from the SELECT-MDS-1 trial and the initial data from the randomized portion of SELECT-AML-1 trial.

About Syros Pharmaceuticals

Syros is committed to developing new standards of care for the frontline treatment of patients with hematologic malignancies. Driven by the motivation to help patients with blood disorders that have largely eluded other targeted approaches, Syros is advancing a robust late-stage clinical 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, and SY-2101, a novel oral form of arsenic trioxide in patients with acute promyelocytic leukemia. Syros is also seeking partnerships for SY-5609, a highly selective and potent CDK7 inhibitor in clinical development for the treatment of select solid tumors, and multiple preclinical 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, SY-2101 and SY-5609, the timing and impact of opening clinical sites, enrolling study participants and reporting clinical data, the pathway to receiving regulatory approval for Syros's drug candidates, the ability to deliver benefit to patients, the intention to seek partnerships for Syros's SY-5609 and oncology discovery programs, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into the second quarter of 2025, 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 Form10-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.

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