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): May 25, 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 May 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 May 25, 2023, the Company issued a press release announcing data from its Phase 1/1b clinical trial ofSY-5609 in advanced solid tumors. 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 May 2023
99.2	Press Release, dated May 25, 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: May 25, 2023

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

Exhibit 99.1

Advancing Novel Treatments for Hematologic Malignancies

May 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 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, 2022 and Syros' Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, each of which is on file with the Securities and Exchange Commission (SEC). 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

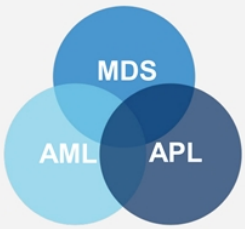
SIGNIFICANT MARKET OPPORTUNITIES IN FRONTLINE

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

STRONG CORPORATE POSITION

Cash runway to fund operations into 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 for the pivotal CR data 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

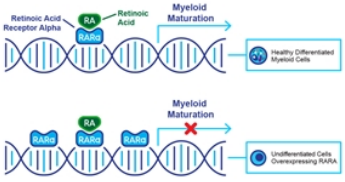
Tamibarotene

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

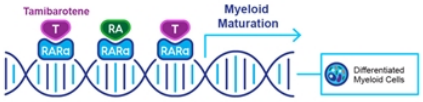
SYROS

Tamibarotene: Compelling profile that addresses large targeted populations

Tamibarotene is a **selective and potent** RARα 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 (AML) 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]

~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

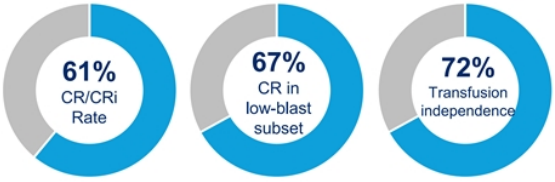
2017

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]

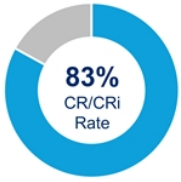


Median time to response: **1.2 months**
Median duration of response: **10.8 months**
Overall survival for complete responders: **18 months**

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

[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

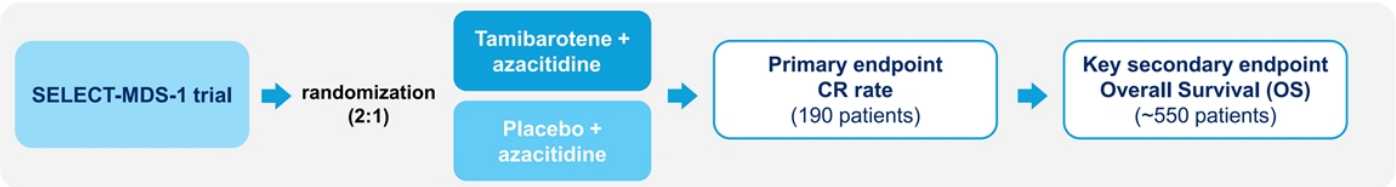
Over 1,000 APL patients treated with tamibarotene[1]	Single agent in AML and MDS patients and doublet (tami/aza) in AML patients[2,3]	Triplet (tami/ven/aza) in AML patients[4]

- 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



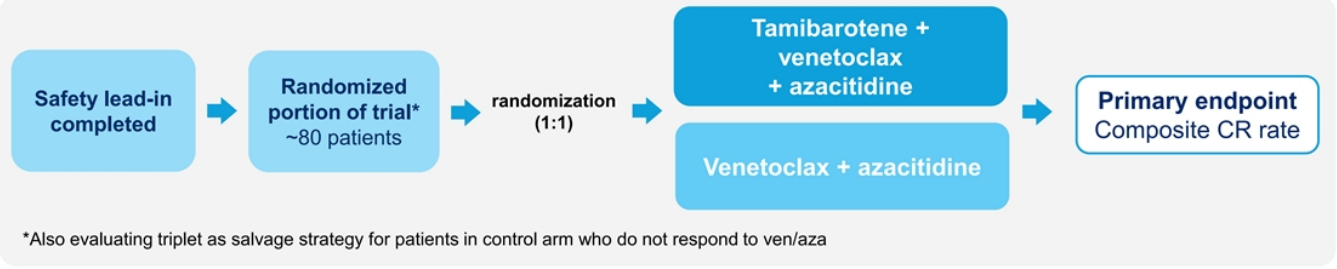
- Robustly designed, double-blind, placebo-controlled study
- 2:1 randomization with one-sided alpha of 0.025
- FDA feedback supports:
  - Focus on population with *RARA* overexpression
  - CR as primary endpoint for approval (full or accelerated) with supporting data on durability of remission
  - Azacitidine as appropriate comparator
- Primary endpoint of CR rate is over 90% powered to detect a difference between experimental and control arms
- Inclusion of OS key secondary endpoint will allow this single trial to efficiently serve as a confirmatory study if needed for full approval
- Fast Track Designation by the FDA

Key Milestones

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

SYROS

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

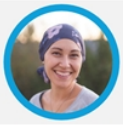
Initiation of randomized SELECT-AML-1 trial	**1Q 23**
Initial data from randomized SELECT-AML-1 trial	**4Q 23**
Additional data from randomized SELECT-AML-1 trial	**2024**

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

SY-2101

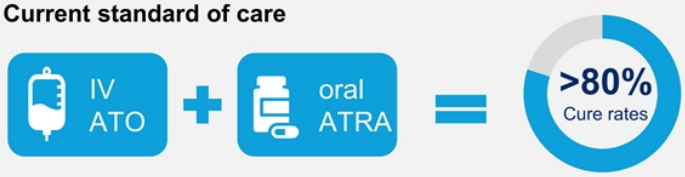
Highly synergistic with our hematology portfolio

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

SYROS

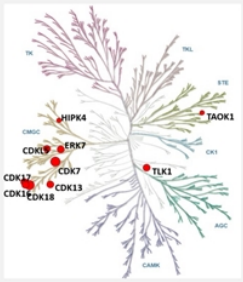
SY-5609

Highly selective and potent oral CDK7 inhibitor

SYROS

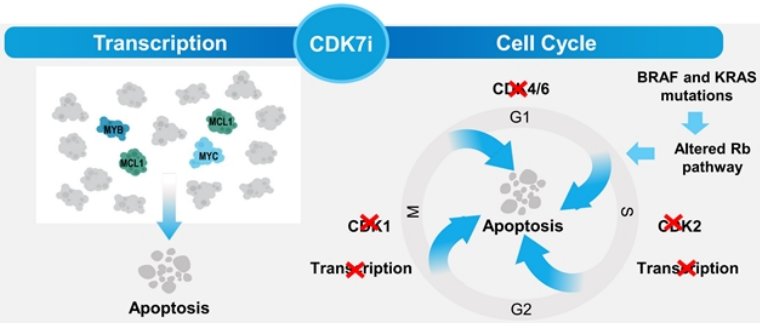
SY-5609: Highly selective and potent oral CDK7 inhibitor

- Phase 1 study in pancreatic cancer, breast cancer and select solid tumors 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, breast cancer 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 in heavily pretreated patients with manageable, predictable tolerability profiles in Phase 1/1b trial

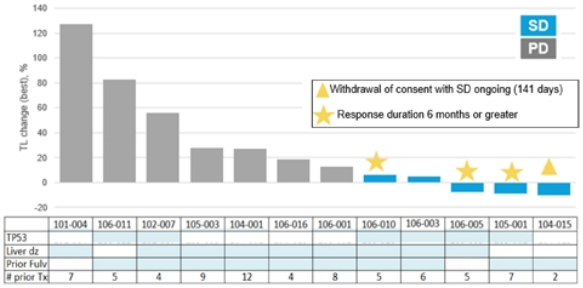
Part 1: Dose escalation evaluating single agent SY-5609 in patients with select advanced solid tumors and in combination with fulvestrant in HR+, HER2- breast cancer

- **MTD of 10 mg** as a single-agent on optimized 7d on/7d off schedule was **well-tolerated** with no DLTs or treatment-related ≥ Gr 3 events. MTD not established in combination with fulvestrant
- **100% DCR at single agent MTD** (3 of 3 patients), with a PDAC patient experiencing a 10% tumor reduction.

Part 2: Combination safety lead-in evaluating SY-5609 and gemcitabine and SY-5609, gemcitabine and nab-paclitaxel in patients with relapsed PDAC

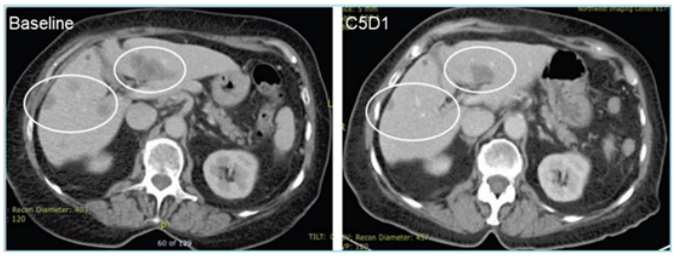
- **MTD of 5mg + Gemcitabine** on 7d on/7d off dosing was **well-tolerated**. MTD not established for the triplet regimen.
- **44% DCR, including a PR** (4 of 9 response-evaluable patients) at doses of 4 and 5mg SY-5609 + gem
- 1 of 2 patients demonstrated **durable SD** with SY-5609 + gem +nab-p

42% DCR in combination with fulvestrant in heavily pre-treated HR+ breast cancer patients



	101-004	106-011	102-007	105-003	104-001	106-016	106-001	106-010	106-003	106-005	105-001	104-015
TP53												
Liver dz												
Prior Fulv												
# prior Tx	7	5	4	9	12	4	8	5	6	5	7	2

PR at 4mg SY-5609 + Gemcitabine: 32% decrease in Target Lesions with ≥ 95% reduction in pancreatic tumor marker CA19-9



Patient off study on C7D1 while still in PR due to non-disease related medical issues

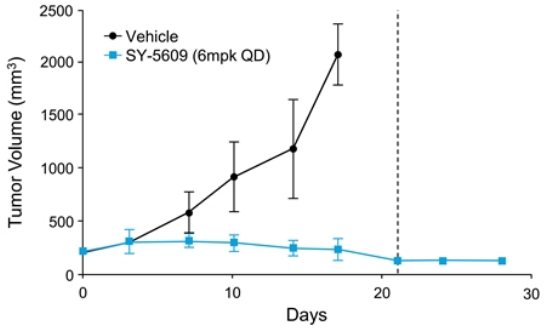
Seeking partnership opportunities for the SY-5609 program

Data presented at 2023 American Society for Clinical Oncology (ASCO) Annual Meeting; *Gemcitabine and nab-pacilitaxel administered at approved doses

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

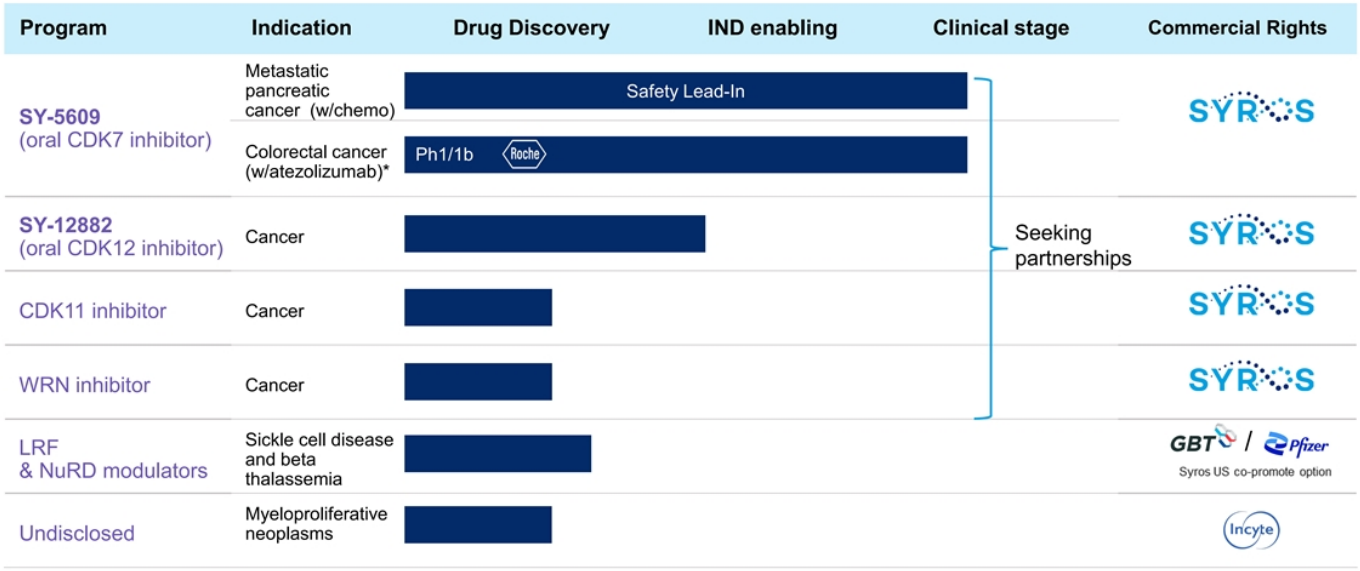
CDK7 inhibition enhances anti-tumor activity of PD-1 inhibition[1]

- 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 2025

Vision

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


SYROS

Exhibit 99.2

Syros Presents Data from Phase 1/1b Clinical Trial of SY-5609 in Advanced Solid Tumors at ASCO Annual Meeting

— New data support further evaluation of SY-5609 for PDAC and HR+ breast cancer and demonstrate significant potential for SY-5609 in a wide range of tumor types and combinations –

— Consistent with prior guidance, exploring partnership opportunities to advance development of SY-5609 —

CAMBRIDGE, Mass., May 25, 2023 – Syros Pharmaceuticals (NASDAQ:SYRS), a biopharmaceutical company committed to advancing new standards of care for the frontline treatment of hematologic malignancies, today announced new clinical data from the Phase 1/1b clinical trial evaluating SY-5609, its highly selective and potent inhibitor of CDK7, in patients with relapsed/refractory pancreatic ductal adenocarcinoma (PDAC), HR+ breast cancer and other solid tumors. The data will be presented in two posters at the 2023 American Society for Clinical Oncology (ASCO) Annual Meeting, taking place June 2-6, in Chicago, Illinois.

"We are pleased to share data from our Phase 1/1b clinical trial of SY-5609, which further reinforce the potential of selective CDK7 inhibition as a potentially transformative approach for difficult-to-treat solid tumors," said David A. Roth, M.D., Chief Medical Officer of Syros. "SY-5609's best in class selectivity and potency produce a predictable, well-managed tolerability profile, and we have optimized an intermittent dosing schedule that we believe enables broad combination potential. Data from both combination cohorts – evaluating SY-5609 in combination with chemotherapy in PDAC and SY-5609 with fulvestrant in HR+ breast cancer – demonstrate an acceptable tolerability profile, as well as promising clinical activity in heavily pre-treated populations that are unlikely to respond to standard of care. Based on these results, we continue to believe that SY-5609 could play a meaningful role in the evolving treatment landscape and are continuing to explore partnership opportunities to maximize the potential of this program."

Syros' Phase 1/1b trial of SY-5609 is a multi-center, open-label study, consisting of two parts: Part 1 is a dose escalation study, evaluating single agent SY-5609 in patients with select advanced solid tumors and in combination with fulvestrant in HR+ breast cancer. Part 2 included a combination safety lead-in designed to inform a dose expansion study, evaluating the doublet regimen of SY-5609 and gemcitabine and the triplet regimen of SY-5609, gemcitabine and nab-paclitaxel in patients with PDAC in their second or third line of treatment.

Data Demonstrate Encouraging Clinical Activity in Patients with PDAC

Syros will present updated data from the single agent dose escalation portion and the gemcitabine/nab-paclitaxel combination safety lead-in portion of the Phase 1/1b trial. The maximum tolerated dose (MTD) of SY-5609 as a single-agent was 10 mg using a 7 day on/7 day off dosing schedule. For the doublet, the MTD was 5 mg SY-5609 plus 1000 mg gemcitabine. A MTD was not established using the triplet cohort of SY-5609, gemcitabine and nab-paclitaxel. Each of the single-agent, doublet and the triplet regimens were generally well-tolerated with mostly low-grade events.

Encouraging clinical activity was observed at the MTDs with SY-5609 both as a single-agent (10 mg) and in combination (4 or 5 mg plus gemcitabine). Among the three response evaluable patients with select solid tumors, which included one patient with PDAC, data demonstrated a 100% disease control rate (DCR) with 10 mg SY-5609 monotherapy, with the PDAC patient experiencing a 10% tumor reduction. Of the nine PDAC patients treated with 4 or 5 mg of SY-5609 in combination with gemcitabine, the data demonstrated a 44% DCR (four patients). The single-agent DCR of 100% is superior to results observed with lower doses of SY-5609 on the 7 day on/7 day off schedule and the doublet DCR of 44% is comparable to current second-line benchmarks.

These data will be presented in a poster titled, "Phase 1/1b study of SY-5609, a selective and potent CDK7 inhibitor, in advanced solid tumors and in 2L/3L pancreatic ductal adenocarcinoma (PDAC) in combination with gemcitabine +/- nab-paclitaxel," on June 3, 2023, 8:00 – 11:00 am CT (9:00 am – noon ET) (Abstract# 3080).

Data Show Promising Early Activity in Patients with Advanced HR+, HER2- Breast Cancer

Syros will present data from the fulvestrant combination cohort. Patients enrolled in this cohort presented with advanced disease: 78.6% (11 of 14 patients) had liver metastases and were heavily pre-treated: 78.6% (11 of 14 patients) had received ≥5 prior therapies, 100% (14 of 14 patients) had progressed on CDK4/6 therapy, and 85.7% (12 of 14 patients) had received prior fulvestrant. The data show that the combination of SY-5609 and fulvestrant demonstrated an acceptable safety profile across a variety of dosing schedules. The adverse event profile of the combination was generally consistent with the safety profile of single agent SY-5609 or fulvestrant, with no new safety signals emerging from the combination at evaluated doses and dosing schedules. An MTD was not established.

Twelve patients were evaluable for response across a range of doses and dosing schedules. Five of 12 achieved stable disease for a DCR of 42%; three of these five patients achieved target lesion regression. Three patients remained on treatment with SD for greater than six months, including patients with the *TP53* mutation, prior fulvestrant exposure and/or liver disease.

These data will be presented in a poster titled, “Tolerability and preliminary activity of the potent, selective, oral CDK7 inhibitorSY-5609 in combination with fulvestrant in patients with advanced hormone receptor-positive (HR+), HER2- breast cancer (BC),” on June 3, 2023, 8:00 – 11:00 am CT (9:00 – noon ET) (Abstract# 3081).

Both posters are now available on the Publications and Abstracts section of the Syros website at www.syros.com.

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, an 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. 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 the commercial potential of SY-5609, its ability to benefit various patient populations, and Syros’s partnership plans with respect to the SY-5609 program. 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: secure a partnership to support the further development of the SY-5609 program; demonstrate in any future clinical trials the requisite safety, efficacy and combinability of SY-5609; sustain the response rates and durability of response seen to date withSY-5609; successfully establish a patient selection strategy to identify patients most likely to benefit from SY-5609; 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, 2022 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, 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.

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