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): December 10, 2022

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 December 2022, 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 December 10, 2022, the Company issued a press release announcing new data presented at the 64th Annual Meeting of the American Society of Hematology from the safety lead-in portion of the Company's ongoing SELECT-AML-1 Phase 2 trial evaluating tamibarotene in combination with venetoclax and azacitidine in newly diagnosed, unfit patients with acute myeloid leukemia and *RARA* gene overexpression. The press release issued in connection with this announcement is attached as Exhibit 99.2 to this Form 8-K and incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.	Description
99.1	Slide Presentation, dated December 2022
99.2	Press Release, dated December 10, 2022
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: December 12, 2022

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

Exhibit 99.1

SYROS

An Expression Makes a World of Difference

December 2022

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 and preclinical 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, 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.

Developing new standards-of-care for the frontline treatment of hematologic malignancies

TARGETED HEMATOLOGY PORTFOLIO

Advancing clinical trials in frontline MDS, AML and APL 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, which include pivotal SELECT-MDS-1 data, randomized SELECT-AML-1 data and initiation of Phase 3 trial in APL

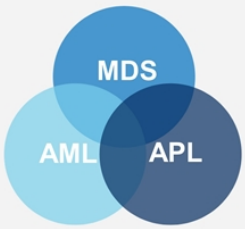
SIGNIFICANT MARKET OPPORTUNITIES IN FRONTLINE

Targeting patient populations underserved by existing options, which are commercially synergistic

STRONG CORPORATE POSITION

Cash runway to fund operations into 2025

3 clinical programs
from our **hematology portfolio**



Advancing our diversified 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, Israel & Russia
	Newly diagnosed unfit AML (w/ven+aza)	SELECT-AML-1 Trial			
SY-2101 (oral ATO)	Newly diagnosed APL (w/ATRA)	Dose confirmation study	Ph3 2H 2023		SYROS
SY-5609 (oral CDK7 inhibitor)	Metastatic pancreatic cancer (w/chemo)	Safety Lead-In			SYROS Seeking partnership opportunities
	Colorectal cancer (w/atezolizumab)*	Ph1/1b Roche			

Tamibarotene is approved in Japan as Amnolake® for patients with relapsed/refractory APL
*Roche-sponsored trial

Multiple value-driving milestones

Tamibarotene in HR-MDS	Pivotal data from SELECT-MDS-1 Phase 3 trial	**4Q23/1Q24**
	Potential NDA filing	**2024**
Tamibarotene in AML	Clinical activity data from safety lead-in SELECT-AML-1 trial	✓
	Initiation of randomized portion of the SELECT-AML-1 trial	**1Q23**
	Data from randomized SELECT-AML-1 trial	**2023/2024**
SY-2101 in APL	PK and safety data	✓
	Initiation of Phase 3 trial	**2H 2023**
SY-5609	Clinical activity data from pancreatic cancer safety lead-in	✓
Discovery	Development candidate named from CDK12 program	✓

Tamibarotene
Selective oral RARα agonist

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Value of Tamibarotene

- Selective and potent RARα agonist; ~50% of MDS patients and ~30% of AML patients are positive for *RARA* gene overexpression
- Ongoing Phase 3 trial in newly diagnosed HR-MDS and Phase 2 trial in newly diagnosed unfit AML patients with RARA overexpression
- Clinical development strategy informed by consistent data from multiple trials demonstrating encouraging clinical activity and safety profile
- Oral drug with novel mechanism and favorable tolerability profile support use in combination and in frontline treatment for those unfit to receive chemotherapy
- Targeting a multi-billion-dollar opportunity in HR-MDS and AML

SYROS

Clinical development strategy reinforced by encouraging, consistent data from multiple trials

Growing body of clinical evidence for tamibarotene

- ✓ Single-agent tamibarotene in R/R HR-MDS patients with *RARA* overexpression showed 60% hematologic response, including one marrow CR[1]
- ✓ Phase 2 data evaluating tamibarotene with azacitidine in ND unfit AML patients with *RARA* overexpression showed:
  - **61% CR/CRi rate**[2]
  - **67% CR rate** in low blast count subset
- ✓ Data from SELECT-AML-1 safety lead-in evaluating tamibarotene with venetoclax and azacitidine in ND unfit AML patients with *RARA* overexpression showed:
  - **83% CR/CRi rate**[3]
- ✓ Safety profile supports ability to use full doses of tamibarotene in combinations with azacitidine in MDS and with venetoclax/azacitidine in AML

→ Tamibarotene in **HR-MDS**

Pivotal data from SELECT-MDS-1 Phase 3 trial **expected late 2023 / early 2024**

→ Tamibarotene in **AML**

Data from randomized portion of SELECT-AML-1 trial Phase 2 trial **expected 2023 / 2024**

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[1] Data presented at ASH 2017; [2] Data presented at ASH 2020; [3] Data presented at ASH 2022

High CR rates, rapid onset of action, and clinically meaningful durability in Phase 2 trial* in newly diagnosed unfit AML with *RARA* overexpression

1.2 months
Time to response

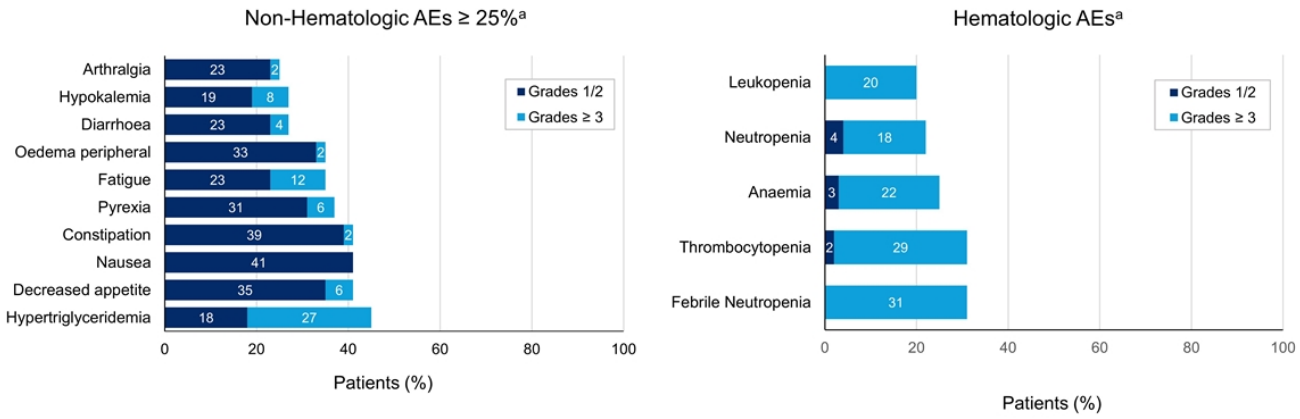
10.8 months
Duration of response

18 months
Overall survival for complete responders

- 89% of CRs were deep molecular or cytogenetic CRs
- Responses seen irrespective of mutation or cytogenetic risk
- Response rates in patients negative for *RARA* overexpression were comparable to historical rates for single-agent aza[1-3]
- 67% of low blast count AML patients achieved CR with tamibarotene/aza
  - 27% of low blast count AML patients negative for *RARA* overexpression achieved CR

*Phase 2 trial evaluating tamibarotene/azacitidine
Data from 18 response evaluable patients with *RARA* overexpression and 28 response evaluable patients negative for *RARA* overexpression presented at ASH 2020 meeting
Data from 6 response-evaluable low blast count AML patients with *RARA* overexpression and 11 response evaluable low blast count AML patients negative for *RARA* overexpression presented at ASH 2020 meeting
[1]Dombret, Blood 2015; [2]Fenaux, JCO 2010; [3]Thepot, American Journal of Hematology 2014

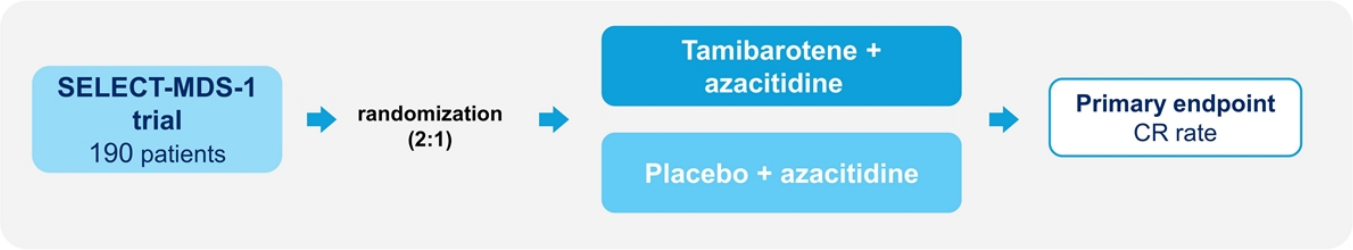
Safety profile supports multiple combinations and long-term use, enhancing opportunity*



- Generally well-tolerated combination in ND unfit AML patients
- No increase in neutropenia, anemia and thrombocytopenia compared to single-agent aza
- Majority of non-hematologic AEs are low grade and reversible

*Phase 2 trial evaluating tamibarotene/azacitidine; data presented at ASH 2020
[a]Includes all enrolled ND unfit patients, N=51.

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

Phase 3 data	4Q23/1Q24
Potential NDA filing	2024

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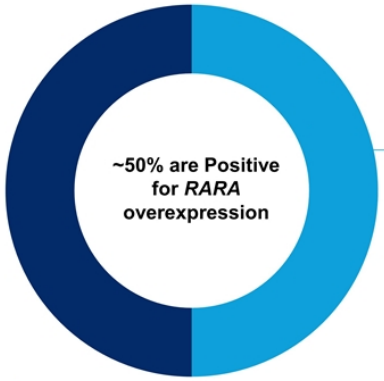
Tamibarotene has the potential to set a new treatment paradigm for HR-MDS patients with *RARA* overexpression

~21,000 newly diagnosed HR-MDS patients in US and EU estimated annually



COMPETITIVE LANDSCAPE OF APPROVED THERAPIES

Targeted Population	All Comers Population
N/A	Azacitidine or decitabine - offers limited efficacy

Syros' Product Candidate

- Patients positive for *RARA* overexpression
- Tamibarotene + aza

Targets ~50% of patients

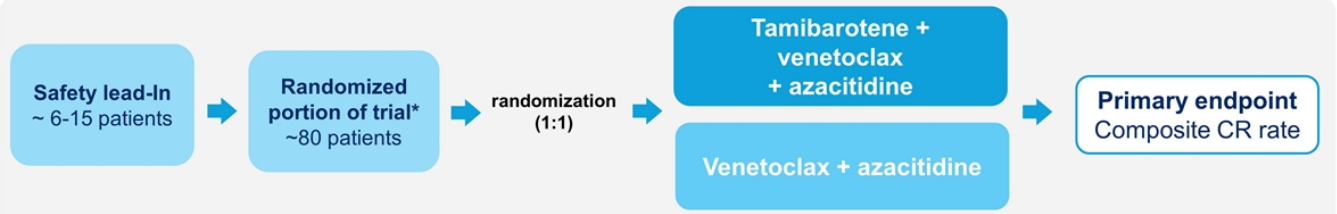
Physicians are familiar with companion diagnostics to determine optimal treatment for AML → Anticipate rapid adaption of targeted therapy in HR-MDS

MDS represents a ~$3.3B* market by 2026

Syros is developing potentially the first therapy for a targeted population in HR-MDS

NOTE:
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
Sources: Decision Resources Group, NCCN guidelines,
*Evaluate Pharma market estimate includes all risk groups for MDS

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

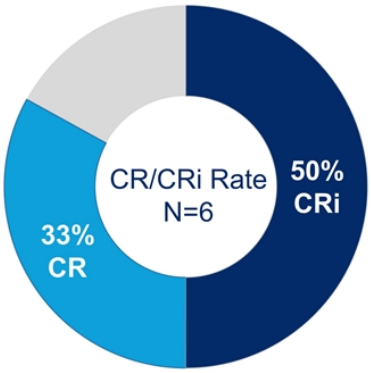
- 30% of patients do not respond to upfront treatment with ven/aza and a majority of those with initial response ultimately relapse
- Venetoclax resistance is associated with monocytic phenotype [1-3]; most patients with *RARA* overexpression, including those who achieved CR/CRi in tamibarotene trial, have this monocytic phenotype[4]

Key Milestones

Safety lead-in data	✓
Randomized data	2023/2024

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

Safety Lead-in of SELECT-AML-1 trial: Safety and response summary



CR/CRi Rate

83%

Median Time to CR/CRi

33 days

(range 25–88 days)

CR = complete response; CRi = CR with incomplete hematologic recovery;

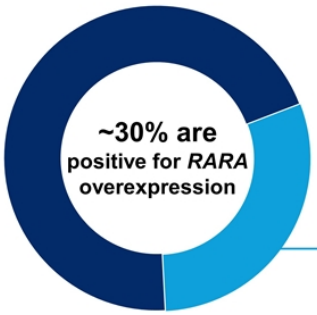
4/5 patients
with CR/CRi had
high monocytic expression score (MES)
associated with venetoclax resistance

Safety Summary:

- Myelosuppression is comparable to reports of venetoclax + azacitidine in this population
- The majority of non-hematologic AEs are low grade and reversible
- SAEs were reported in 6 patients; the most frequent (occurring in ≥ 2 pts) included febrile neutropenia (4 pts) and pneumonia (3 pts)
- Median duration of therapy was 76.5 days (20-104); Median duration of follow-up was 107 days (56-314)

Tamibarotene targets patients with *RARA* overexpression which represents one of the largest targeted populations in unfit AML

~25,000 Newly Diagnosed Unfit AML Patients in US and EU



COMPETITIVE LANDSCAPE OF APPROVED THERAPIES

Targeted Populations

- FLT3+: XOSPATA® (r/r) — *Targets ~30% of patients*
- IDH1+: TIBSOVO ® — *Targets ~8% of patients*
- IDH2+: IDHIFA® — *Targets ~11% of patients*

Syros' Product Candidate

- *RARA*-positive
- Tamibarotene + ven/aza

Targets ~30% of patients

All Comers Populations

- HMA[1] + venetoclax
- LDAC + glasdegib

~1/3 of patients do not respond to standard of care ven/aza and majority of those with initial response ultimately relapse.

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

Epidemiology: DRG. Market sizing: Evaluate Pharma NOTE*: market estimate includes all AML (fit and unfit)
Prevalence of RARA-positive patients based on data presented at ESH 2017 and ESH 2019; Resistant Ven population - Dinardo, NEJM 2020; Dinardo, Blood 2019
Prevalence and Clinical Effect of IDH1 and IDH2 Mutations Among Cytogenetically Normal Acute Myeloid Leukemia Patients, Clin Lymphoma Myeloma Leuk. 2015 Sep;15(9):550-5.
Daver N, Schlenk RF, Russell NH, et al. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299–312.

SY-2101
Novel oral form of arsenic trioxide

SYROS

Value of SY-2101

- Novel oral form of arsenic trioxide (ATO) with opportunity to replace standard of care for APL patients; APL is approximately 10% of all AML patients
- Orally bioavailable with exposures consistent with IV ATO
- Clear development path to approval in front-line APL
- Potential for rapid adoption in front-line APL, including specialized commercial effort and synergies with tamibarotene

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Clear development path in frontline APL

- Based on preliminary data as of July 2022 from dose confirmation study:
  The first cross-over data directly comparing SY-2101 to the approved dose of IV ATO
  - SY-2101 administered at 15 mg achieved exposures comparable to IV ATO administered at 0.15 mg/kg based on Cmax and AUC parameters
  - SY-2101 showed high oral bioavailability of ~80%
  - Continues to support favorable tolerability and safety profile
- FDA feedback from November 2021 supports:
  - Molecular CR as primary endpoint compared to historic data for accelerated approval
  - Event free survival (EFS) as primary endpoint compared to historic data for full approval
  - IV ATO arm for safety comparison
- In July 2022, received feedback from EMA, which together with prior FDA feedback, informs decision to move forward with single registration trial that could support approval of 2101 in the US and EU

Key Milestones

Initiation of Phase 3 trial	2H 2023

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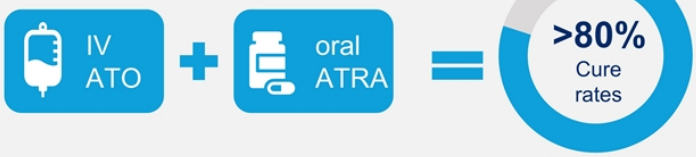
SY-2101 offers significant opportunity to reduce treatment burden, increase access, reduce health care costs and utilization

Current standard of care



Treatment burden:
Current course of treatment involves infusions of

up to 140 x 2-4 hrs

over nearly a year

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

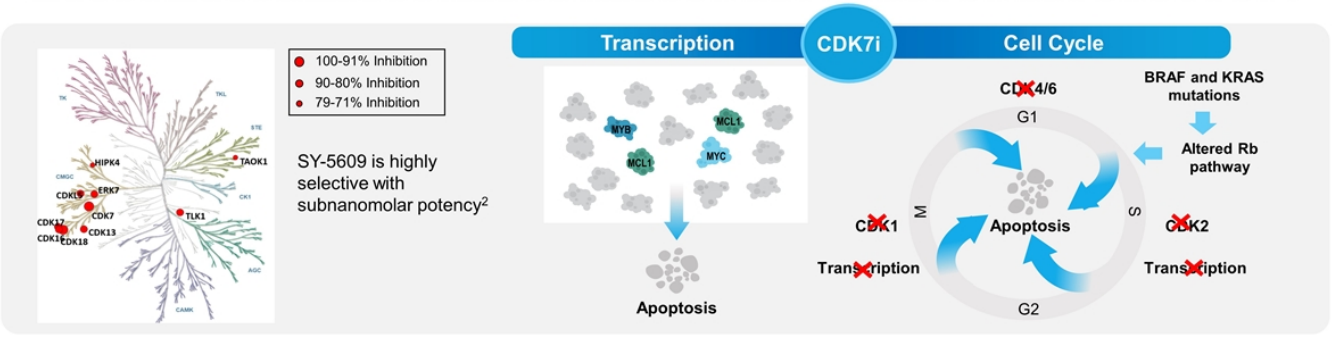
NCCN AML treatment guidelines (Nov 2020)
Trisenox (arsenic trioxide) USPI

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
  MTD not yet reached with optimized dosing[1], and dose escalation is continuing
- Well tolerated safety profile in combination with predominantly low grade AEs;
- Broad potential in multiple difficult to treat cancer populations, including PDAC and CRC



[1]MTD not yet reached as of October 2022
[2]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

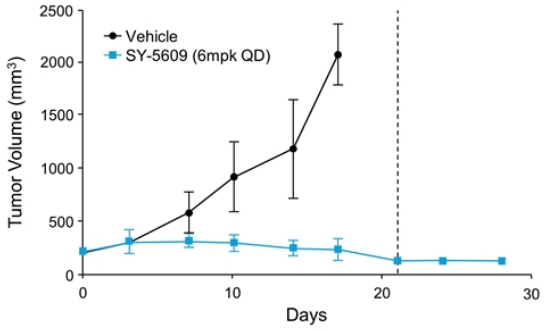
Continued dose escalation of SY-5609 to 15 mg as a single agent and to 10 mg with gemcitabine planned

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 as single agent



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

Key Milestones:

- Roche is now 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

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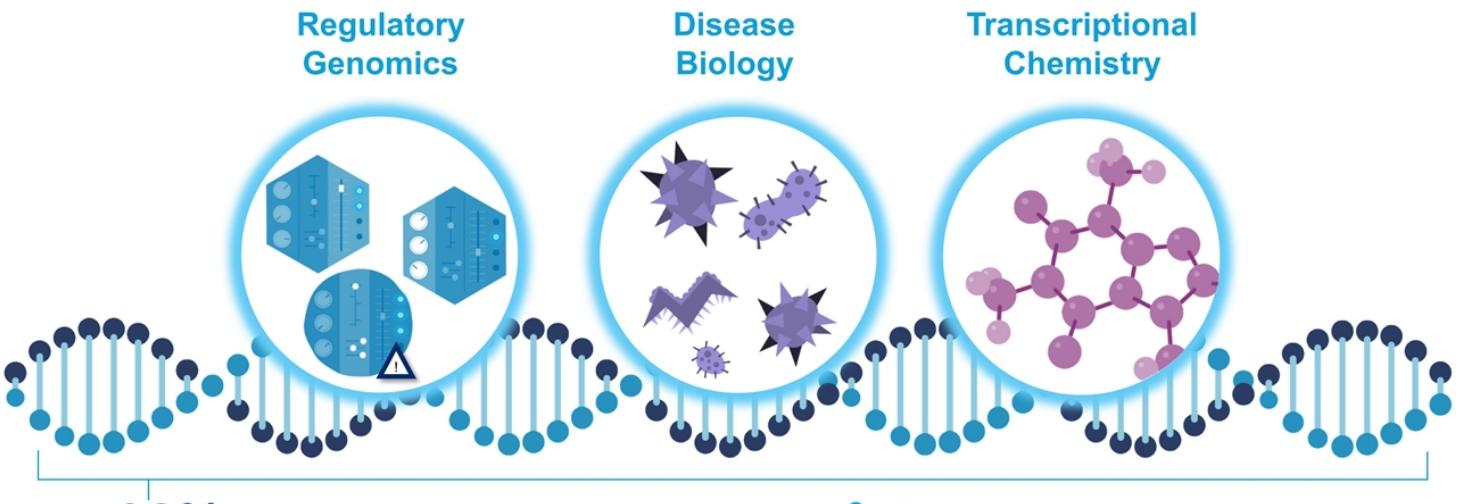
CRC data presented in May 2020 at ASCO Virtual Symposium.

1. Zhang et al., 2020, Cancer Cell 37, 1-18

Gene Control Discovery Engine

SYROS

Redefining the power of small molecules to control expression of genes



98% Previously unexplored regulatory regions of the genome control expression of genes determining cell function; majority of disease variation found in these regions

Patient Impact

Medicines that control the expression of genes to provide profound benefit for patients with severe diseases

SYROS

Seeking partnerships for our oncology discovery programs

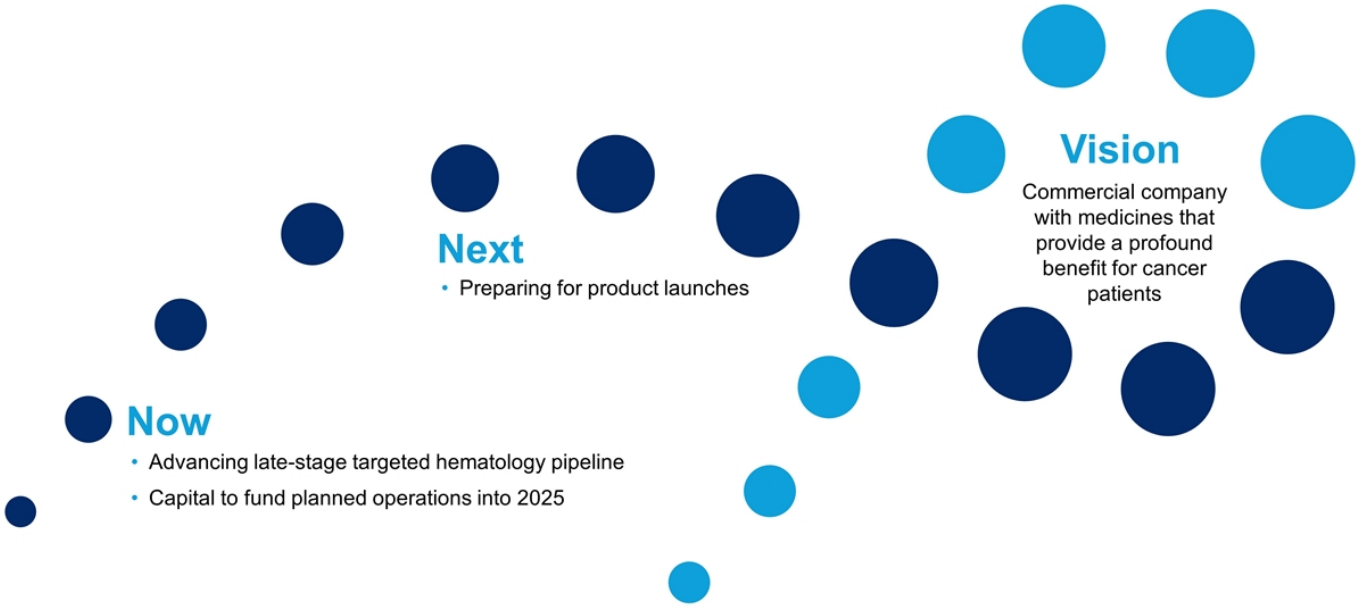
ONCOLOGY

Program	Target Development	Drug Discovery	IND-enabling	Commercial Rights
CDK12 inhibitor				SYROS
CDK11 inhibitor				SYROS
WRN inhibitor				SYROS

PARTNERED PROGRAMS

Program	Target Development	Drug Discovery	IND-enabling	Commercial Rights
Sickle cell disease & beta thalassemia				GBT Syros US co-promote option
Myeloproliferative neoplasms				Incyte

Rapidly advancing toward our vision



Now

- Advancing late-stage targeted hematology pipeline
- Capital to fund planned operations into 2025

Next

- Preparing for product launches

Vision

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

SYROS


SYROS

Exhibit 99.2

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., December 10, 2022 – 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 from25-88).
- Median duration of treatment was 76.5 days (ranging from20-104) 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 theSELECT-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 atwww.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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