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 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, we intend to conduct meetings with third parties in which our current corporate slide presentation is presented. A copy of this slide presentation, dated January 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 January 10, 2022, we issued a press release announcing our 2022 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 2022.
99.2	Press Release dated January 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: January 10, 2022

By: /s/ Gerald E. Quirk
Gerald E. Quirk
Chief Operations Officer

Exhibit 99.1

SYROS

An Expression Makes a World of Difference

January 2022

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, research and clinical development plans, collaborations, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. 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 our ability to: advance the development of our programs, including tamibarotene, SY-2101 and SY-5609, under the timelines we project in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of our drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; obtain and maintain patent protection for our 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, including our ability to perform under our collaboration agreements with Incyte Corporation and Global Blood Therapeutics; manage competition; manage expenses; raise the substantial additional capital needed to achieve our business objectives; attract and retain qualified personnel; and successfully execute on our business strategies; risks described under the caption “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2020 and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, each of which is on file with the Securities and Exchange Commission (SEC); and risks described in other filings that we may make with the SEC in the future.

In addition, the extent to which the COVID-19 outbreak 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 outbreak, 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 presentation speak only as of the date this presentation is made, and we expressly disclaim any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

Advancing to become a fully integrated biopharmaceutical company with late-stage clinical programs

TARGETED HEMATOLOGY PORTFOLIO

Advancing clinical-stage trials with the potential to set new standards of care

SELECTIVE CDK INHIBITOR PORTFOLIO

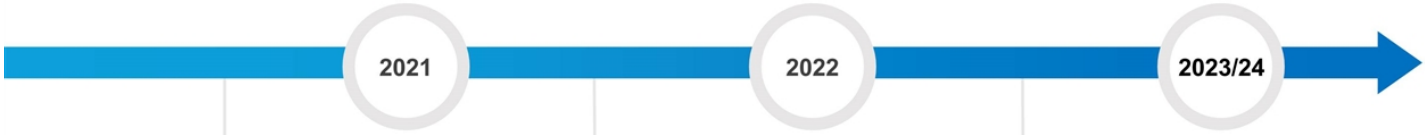
Advancing in indications where there is a high unmet need as well as strong clinical/preclinical data and mechanistic rationale

GENE CONTROL DISCOVERY ENGINE

Leveraging our expertise in regulatory genomics, disease biology, and transcriptional chemistry to address disease-causing alterations in gene expression

3 clinical programs from our **hematology and CDK portfolios,** as well as a robust **gene control discovery engine**

Significant clinical progress and upcoming data readouts position us well to achieve our vision



Tamibarotene

2021:
- ✓ Initiation of SELECT-MDS-1 Phase 3 trial
- ✓ Initiation of SELECT-AML-1 Phase 2 trial

2022:
- **Safety lead-in data** from SELECT-AML-1 Phase 2 trial in 2H 2022

2023/24:
- **Pivotal data** from SELECT-MDS-1 Phase 3 trial in 4Q23/1Q24
- Potential NDA filing for HR-MDS in 2024
- **POC data** from SELECT-AML-1 Phase 2 trial

SY-2101

2021:
- ✓ Initiation of SY-2101 dose confirmation study

2022:
- **PK and safety data** from SY-2101 dose confirmation study in mid-2022

2023/24:
- Initiation of SY-2101 Phase 3 trial in 1Q 2023

SY-5609

2021:
- ✓ Reported promising initial safety and POA data from Phase 1 SY-5609 trial
- ✓ Initiation of PDAC expansion cohort

2022:
- **Safety lead-in data** from expansion cohort in pancreatic cancer in 2H 2022
- Initiation of SY-5609 Phase 1 trial in heme malignancies in 2H 2022
- Roche plans for SY-5609/atezolizumab arm of its Phase 1/1b INTRINSIC study to be open for enrollment in 1H 2022

2023/24:
- **Initial data** from SY-5609 Phase 1 trial in heme malignancies in mid-2023
- **POC data** from pancreatic cancer cohort

SYROS

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 1Q 2023		SYROS
SY-5609 (oral CDK7 inhibitor)	Metastatic pancreatic cancer (w/ chemo)	Expansion Cohort			SYROS
	R/R Hematology malignancies	Ph1 2H 2022			
	Colorectal cancer (w/atezolizumab)*	Ph1/1b 1H 2022 Roche			

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

Tamibarotene
Selective oral RARα agonist

SYROS

Value of Tamibarotene

- Selective and potent RARα agonist; ~30% of AML and HR-MDS patients are RARA-positive
- RARA biomarker discovered from Syros' gene control discovery engine
- Ongoing Phase 3 trial in newly diagnosed HR-MDS, potentially the first therapy for a targeted population in HR-MDS with broad potential in RARA-positive patients
- Oral drug with novel mechanism and favorable tolerability profile supports use in combination and in front-line treatment for those unfit to receive chemotherapy
- Targeting a multi-billion-dollar opportunity in HR-MDS and AML

SYROS

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

1.2 months
Time to response

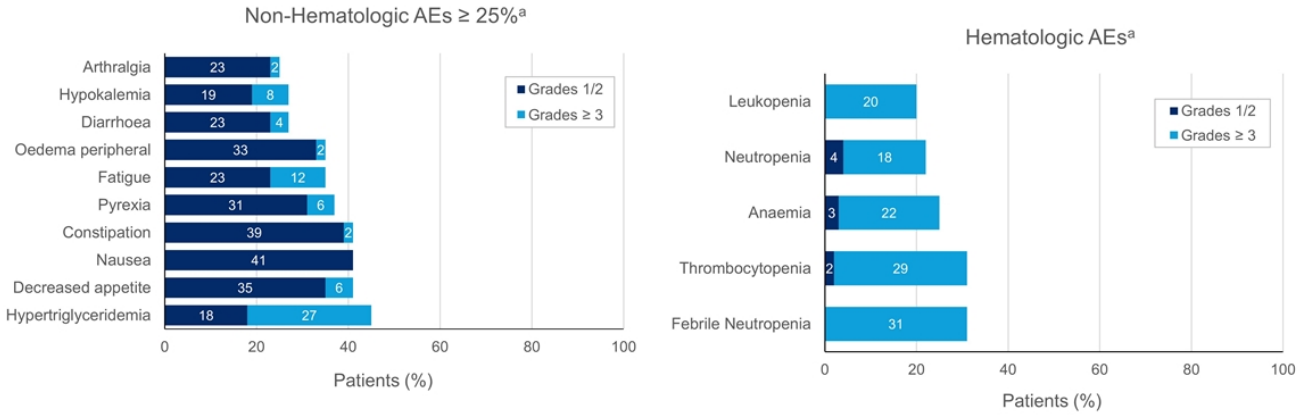
10.8 months
Duration of response

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 RARA-negative patients comparable to historical rates for single-agent aza[1-3]
- 67% of low blast count AML patients achieved CR with tamibarotene/aza
  - 27% of RARA-negative low blast count AML patients achieved CR

Data from 18 response evaluable RARA-positive and 28 response evaluable RARA-negative patients presented at ASH 2020 meeting
Data from 6 response-evaluable RARA+ low blast count AML patients and 11 response evaluable RARA-negative low blast count AML patients presented at ASH 2020 meeting
[1]Dombret, Blood 2015; [2]Fenaux, JCO 2010; [3]Thepot, American Journal of Hematology 2014

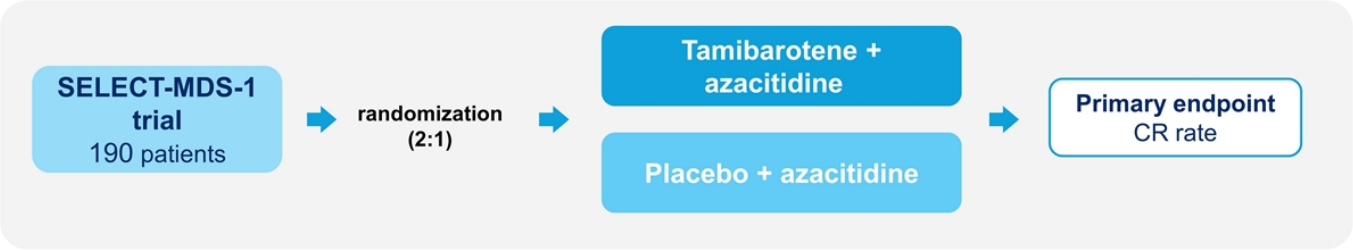
Safety profile supports multiple combinations and long-term use, enhancing opportunity



- 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

[a]Includes all enrolled ND unfit patients, N=51.
Data presented at ASH 2020 meeting

Ongoing SELECT-MDS-1 Phase 3 trial in RARA-positive newly diagnosed HR-MDS



- 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 RARA+ population
  - CR as primary endpoint for approval
  - Azacitidine as appropriate comparator

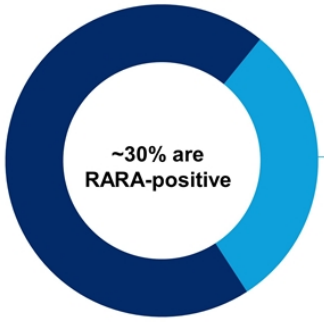
Key Milestones

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

SYROS

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

~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

RARA+

Tamibarotene + aza

Targets ~30% of patients

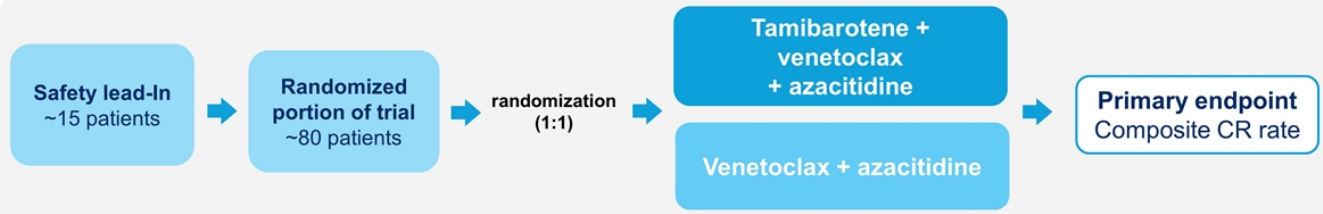
Physicians are familiar with companion diagnostics to determine optimal treatment for AML → Anticipate rapid adaption of targeted therapy in HR-MD

MDS represents a ~$3.3B* market by 2026

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

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

Ongoing SELECT-AML-1 Phase 2 trial of triplet regimen in ND RARA-positive unfit AML patients



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

Translational data support potential for RARA 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 RARA+ patients, including those who achieved CR/CRi in tamibarotene trial, have this monocytic phenotype[4]

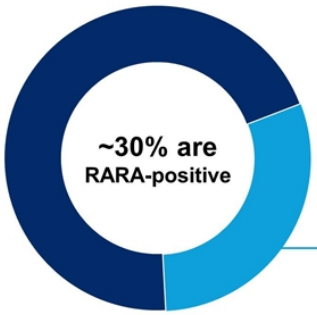
Key Milestones

Trial initiated	3Q 2021
Safety lead-in data	2H 2022

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

Tamibarotene targets RARA-positive patients 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+
  - Tamibarotene + 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
- Potential ~$250+ million market opportunity based on current pricing for IV ATO

Clear development path in front-line APL

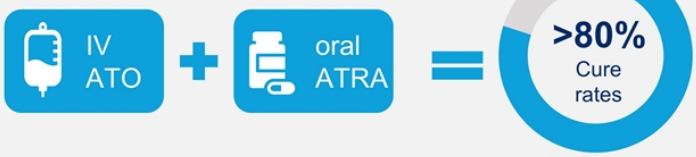
- Dose confirmation study evaluating PK and food effect using C_{max} and AUC, and tolerability to identify optimal dose for Phase 3 trial
- FDA feedback from November 2021 supports:
  - Molecular CR as primary endpoint compared to historic data for accelerated approval
  - Event free survival (EFS) as primary endpoint compared to historic data for full approval
  - IV ATO arm for safety comparison

Key Milestones

PK and safety data	Mid-2022
Initiate Phase 3 trial	1Q 2023
Phase 3 data	2025

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

Potential ~$250+ million

opportunity based on current pricing for IV ATO[1]

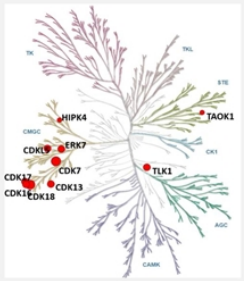
NCCN AML treatment guidelines (Nov 2020)
Trisenox (arsenic trioxide) USPI
[1]IBM Truven Redbook pricing for Trisenox

SY-5609
Highly selective and potent oral CDK7 inhibitor

SYROS

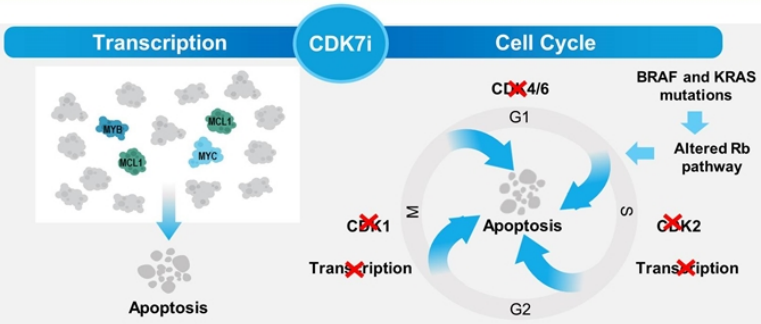
SY-5609: Highly selective and potent oral CDK7 inhibitor

- Strong pre-clinical data support potential across a range of difficult-to-treat solid tumors and blood cancers
- Demonstrated proof of activity and proof of mechanism in refractory solid tumor patients with a generally favorable tolerability profile. Preclinical/clinical data of CDK7 inhibition support plans in PDAC, CRC, and blood cancers
- Further validates Syros' gene control discovery engine



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

SY-5609 is highly selective with subnanomolar potency[1]



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[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

Phase 1 dose escalation study: Favorable tolerability profile with predominantly low-grade AEs

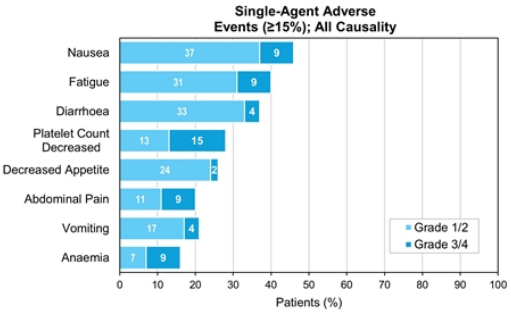
Patient Population

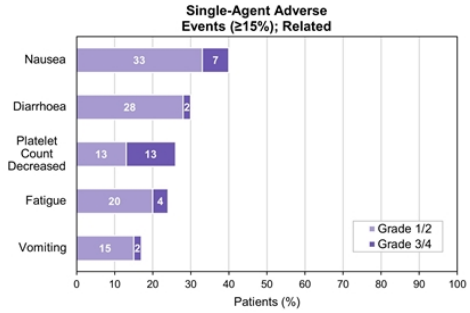
Enrolled patients with advanced breast, colorectal, lung, ovarian or pancreatic cancer, as well as other tumor types with Rb pathway alterations; heavily pretreated with as many as eight prior therapies and a median of four prior therapies

Objectives

Safety, tolerability, PK, PD (POLR2A), antitumor activity

Tolerability was optimized with 7d on/7d off dosing schedule

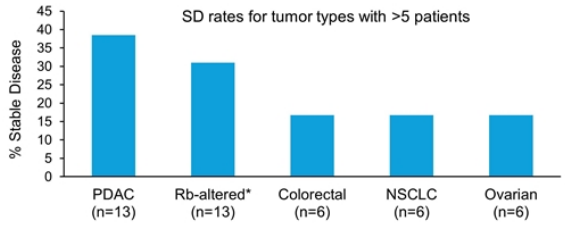




- Manageable safety profile with majority of AEs low-grade and reversible
- Low rate of discontinuation due to AEs at ~7%
- MTD not yet reached at 7d on/7d off with dosing up to 6 mg
- Induction of PD marker in patients treated at 3 mg and above reached levels associated with tumor regressions in preclinical models and with target lesion reductions in study

Clinical activity seen in heavily pretreated patients; strongest in PDAC, Rb-altered and KRAS-mutant cancers

Highest rates of activity seen in pancreatic cancer patients and Rb-altered tumor cohort[1]



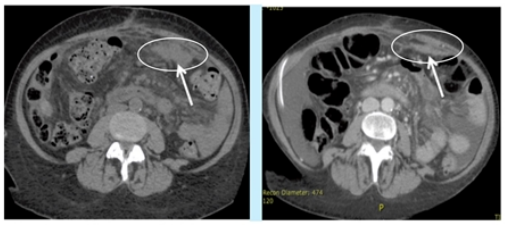
*Rb-altered patients had tumor types other than breast, ovarian, CRC, lung or pancreatic cancer, who were enrolled based on historical molecular evidence of mutation/deletion in Rb pathway gene(s).

- 13 of 45 (28.9%) of response evaluable patients achieved stable disease (SD), 6 had tumor regressions of up to 20%
- 5 of 13 (38.5%) of response-evaluable PDAC patients achieved SD, 2 with tumor shrinkage
  - 3 of 4 PDAC pancreatic cancer patients with serial CA-19-9 data had decreases (32-72%) in this clinically relevant tumor marker
- 58% of the SD patients with mutation data had KRAS mutations compared to 32% with PD
  - 67% of patients with SD who also had tumor shrinkage had KRAS mutations

Heavily pretreated pancreatic cancer patient in 3rd relapse achieve durable SD and significant tumor marker reduction of 72%

- Scan showed 20% decrease in target lesion
- Remained in SD for 10 months
- Received 3mg/day on 7d on/7d off schedule for 7+ months on treatment

CT scans show 20% decrease in target lesion



Courtesy, START San Antonio

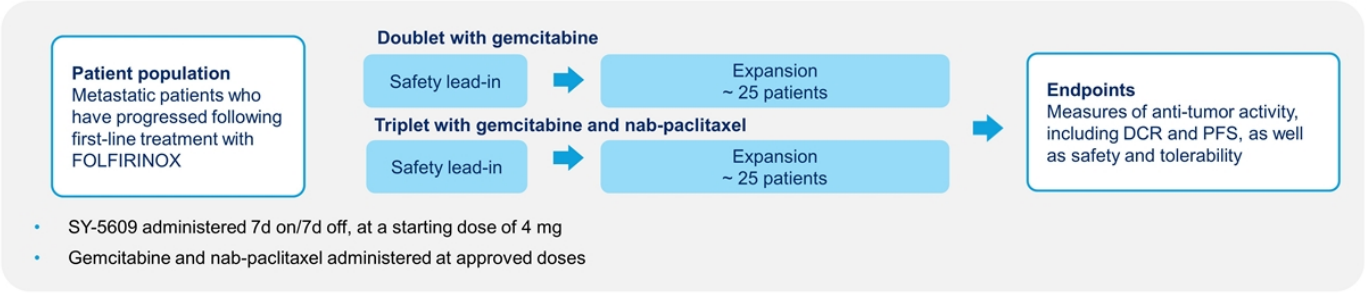
SYROS

Data presented at ESMO 2021
[1]Internal company data

Exploring SY-5609 in three distinct approaches based on mechanistic rationale, preclinical data and clinical signals

Pancreatic Cancer	BRAF-mutant Colorectal Cancer	Hematologic Malignancies
• KRAS mutations are ubiquitous and powerful activators of cell signaling and transcriptional programs • Compelling preclinical data and synergy with gemcitabine • Single agent SY-5609 showed: - Clinical activity in relapsed refractory pancreatic cancer and Rb-altered tumors - KRAS mutations associated with clinical activity	• BRAF mutations, present in 10% of colorectal cancer patients, are powerful activators of cell signaling and transcriptional programs • Compelling preclinical data as single agent • CDK7 inhibition enhances anti-tumor activity of immunotherapy in preclinical models	• Genetics of heme malignancies point to multiple oncogenic transcriptional, epigenetic, and cell cycle control drivers • CDK7 inhibitors demonstrate robust preclinical activity as a single agent and in combination, supporting the potential in a broad range of blood cancers • First clinical investigation of CDK7 inhibitor in hematologic malignancies

Ongoing expansion cohort in relapsed pancreatic patients provides opportunity to address a high unmet need



- SY-5609 administered 7d on/7d off, at a starting dose of 4 mg
- Gemcitabine and nab-paclitaxel administered at approved doses

High unmet need in metastatic pancreatic cancer

- Incidence of second-line patients is ~27,500 in US[1]
- Only approved second-line therapy (Onivyde® + 5-FU/LV) has PFS of 3.1 months[2]

Key Milestones

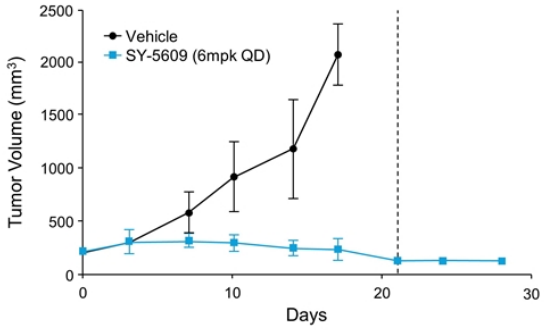
Trial initiated	4Q 2021
Safety lead-in data	2H 2022

[1]Sadhu and Vinuesa, Pancreatic Cancer Disease Landscape & Forecast, DRG, 2021.; [2]Wang-Gillam et al, 2015.;

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 plans for SY-5609/atezolizumab arm of its Phase 1/1b INTRINSIC trial to be open for enrollment in 1H 2022
- 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., 2020, Cancer Cell 37, 1-18

Leveraging expertise in hematology with planned Phase 1 study of SY-5609 in R/R hematologic malignancies

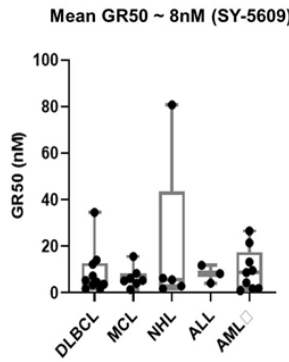
SY-5609 dose escalation study in R/R heme malignancies:

Phase 1 single agent trial → **Endpoints**: Include safety, tolerability, and clinical activity

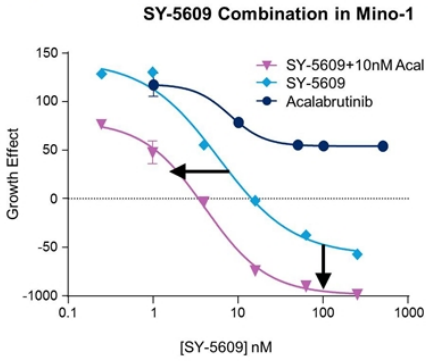
Key Milestones

Initiation of trial	2H 2022
Initial data	Mid-2023

SY-5609 highly active in a diverse heme cell line panel heme



SY-5609 is synergistic with BTK inhibitor in MCL cell line *in vitro*

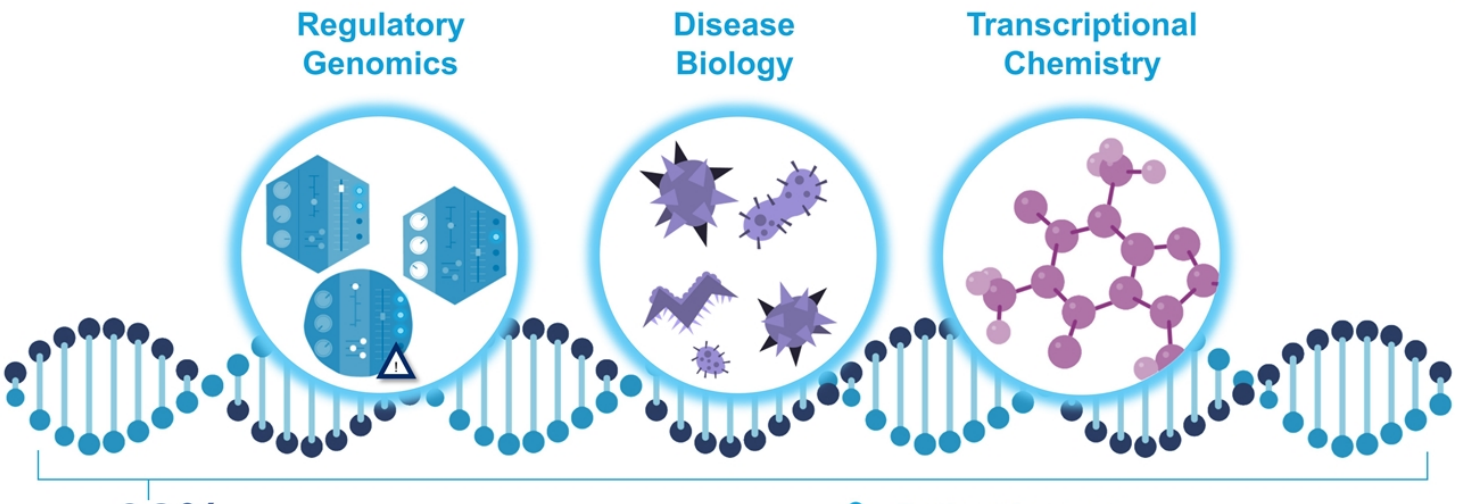


- B cell lymphomas have multiple oncogenic transcriptional, epigenetic, and cell cycle control drivers.
- AML associated with alterations in the mitochondrial apoptosis pathway relating to DNA damage and cell cycle progression
- CDK7 inhibitors reduces expression of MCL1, an anti-apoptotic protein
- In preclinical studies, CDK7 inhibitors have shown:
  - Low nM potency in leukemia & lymphoma cell lines
  - Robust single agent *in vivo* activity in DLBCL, MCL, and AML models
  - Synergy with BTKi and venetoclax

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

Robust early-stage oncology pipeline to fuel long-term growth

ONCOLOGY

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

PARTNERED PROGRAMS

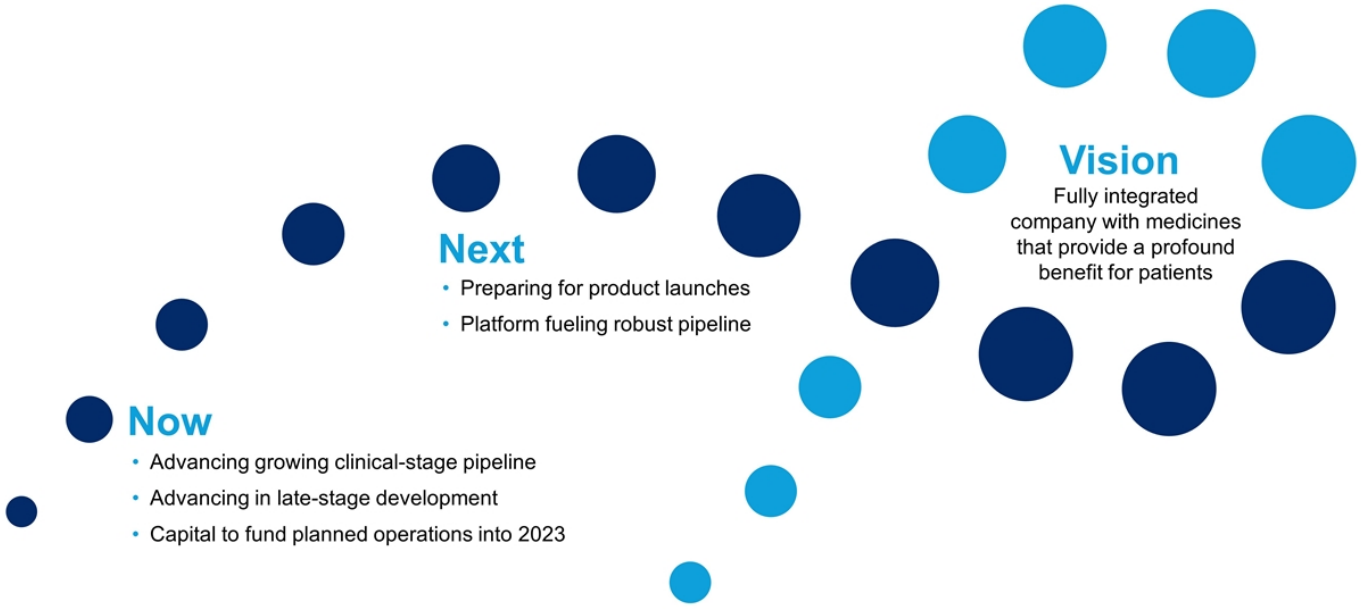
Program	Target Development	Drug Discovery	IND-enabling	Commercial Rights
Sickle cell disease & beta thalassemia				GBT Syros US co-promote option
Myeloproliferative neoplasms				Incyte

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	Safety lead-in data from SELECT-AML-1 trial	**2H 2022**
SY-2101 in APL	PK and safety data	**Mid-2022**
	Initiate Phase 3 trial	**1Q 2023**
	Data from Phase 3 trial	**2025**
SY-5609	Safety lead-in data in pancreatic cancer	**2H 2022**
	Initiate Phase 1 trial in R/R hematologic malignancies	**2H 2022**
	Initial data from Phase 1 trial in R/R hematologic malignancies	**Mid-2023**
Discovery	Development candidate named from CDK12 program	**2H 2022**

SYROS

Rapidly advancing toward our vision



Now

- Advancing growing clinical-stage pipeline
- Advancing in late-stage development
- Capital to fund planned operations into 2023

Next

- Preparing for product launches
- Platform fueling robust pipeline

Vision

Fully integrated company with medicines that provide a profound benefit for patients

SYROS

Appendix

Preclinical data support SY-5609 in relapsed pancreatic cancer patients in combination with chemotherapy

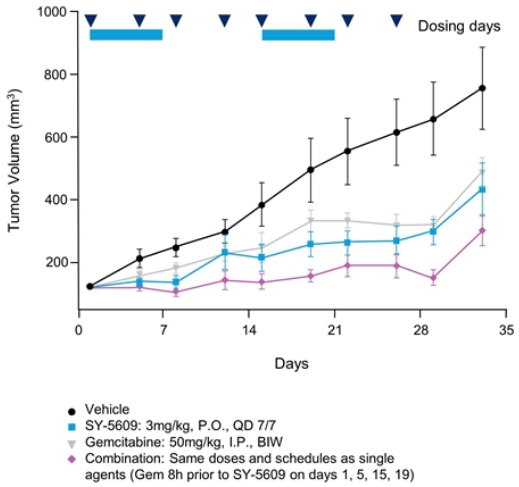
SY-5609 induced regressions in KRAS-mutant models, including those derived from heavily pretreated patients

Model ID	TGI (%)	Prior treatments	KRAS mutation
1	>100	0	G12D
2	>100	3	NRAS
3	>100	5	G12D
4	>100	3	G12D
5	92	0	G12V
6	87	0	G12V
7	42	4	G12D
8	8	0	G12R

Dosed at 6mg/kg QD for 21 days

- Regressions seen in 50% (4/8) models
  - 3/4 models with regressions derived from heavily pretreated patients

SY-5609 potentiated activity of gemcitibine in pancreatic cancer model using 7d on/7d off regimen




SYROS

Syros Announces Clinical Updates and 2022 Goals to Support its Advancement to a Fully Integrated Biopharmaceutical Company

Initiated Expansion Cohort of SY-5609 with Chemotherapy in Pancreatic Cancer Patients
Expects to Report Data from Three Clinical Trials Across Hematology and Selective CDK Inhibitor Programs in 2022
Now Expects to Initiate Phase 1 Single Agent Trial ofSY-5609 in Hematologic Malignancies in 2H 2022
Expects to Nominate Development Candidate from CDK12 Program in 2H 2022

CAMBRIDGE, Mass., January 10, 2022 – Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today provided an update on its clinical development programs and outlined its strategic priorities and upcoming expected milestones.

"2022 promises to be a transformative year as we continue to advance our studies of tamibarotene,SY-2101, and SY-5609. We are looking forward to three clinical data readouts this year as well as pivotal data from the SELECT-MDS-1 trial in late 2023 or early 2024," said Nancy Simonian, M.D., Syros' Chief Executive Officer. "Additionally, in the second half of this year we expect to nominate our new development candidate from our CDK12 program, highlighting the productivity of our gene control discovery engine and our expertise in CDK inhibition. Together, we believe these upcoming milestones will provide insight into the clinical potential of our development-stage assets and lay the foundation for our long-term growth as we advance Syros into a fully integrated biopharmaceutical company."

Dr. Simonian continued, "We are pleased with our recent interactions with the U.S. Food and Drug Administration on the Phase 3 clinical trial design of SY-2101, which we now expect to initiate in the first quarter of 2023. In addition, based on preclinical data that supports CDK7 inhibition's potential across a range of hematologic malignancies, we expect to start in the second half of this year a Phase 1 single agent study of SY-5609 in patients with relapsed blood cancers, including B-cell lymphomas, prior to moving into specific indications. We are excited to be the first company to advance a CDK7 inhibitor into hematology clinical development. The trial results have potential to benefit a broader patient population as well as demonstrate CDK7 inhibition as a novel approach for many difficult-to-treat hematologic cancers."

CLINICAL PROGRAM UPDATES AND UPCOMING MILESTONES

Targeted Hematology

Tamibarotene: Oral RARa agonist

Syros is evaluating tamibarotene in patients with RARA-positive newly diagnosed higher-risk myelodysplastic syndrome(HR-MDS). The Company expects to report data from the ongoing SELECT-MDS-1 Phase 3 trial evaluating tamibarotene in combination with azacitidine inHR-MDS in the fourth quarter of 2023 or first quarter of 2024, with a potential NDA filing expected in 2024.

Syros is also evaluating tamibarotene for the treatment of patients with RARA-positive newly diagnosed unfit acute myeloid leukemia (AML). The Company expects to report data from the safety lead-in portion of the ongoing SELECT-AML-1 Phase 2 trial evaluating tamibarotene in combination with azacitidine and venetoclax in the second half of 2022.

SY-2101: Oral arsenic trioxide (ATO)

Syros is evaluating SY-2101 in patients with newly diagnosed acute promyelocytic leukemia (APL). The Company expects to report PK and safety data from its ongoing dose confirmation trial in mid-2022. The feedback from a Type C meeting with the U.S. Food and Drug Administration (FDA) in November 2021 continues to support molecular complete response rate as the primary endpoint for accelerated approval and event free survival as the primary endpoint for full approval, in each case compared to historic IV ATO data. Additionally, based on the feedback, Syros now expects the trial to enroll approximately 215 patients randomized two to one to receive SY-2101 or intravenously administered (IV) ATO. The IV ATO arm will allow safety and tolerability comparisons. Syros now expects to initiate the Phase 3 trial in the first quarter of 2023 and to announce data in 2025.

Selective CDK Inhibition

SY-5609: Oral CDK7 inhibitor

In the fourth quarter of 2021, Syros initiated the expansion cohort evaluating SY-5609 in combination with chemotherapy in patients with second-line metastatic pancreatic cancer. The cohort is expected to enroll approximately 50 pancreatic cancer patients who have progressed following first-line treatment with FOLFIRINOX. Patients will receive either SY-5609 in combination with gemcitabine, or SY-5609 in combination with gemcitabine and nab-paclitaxel, at the approved doses of the combination agents. The study will evaluate safety and tolerability, as well as efficacy measures such as disease control rate and progression free survival. Syros expects to report safety lead-in data of SY-5609 in combination with chemotherapy in the second half of 2022.

Syros also plans to evaluate the potential ofSY-5609 in hematologic tumors. Based on mechanistic rationale and preclinical data, which support the potential of CDK7 inhibition in a broad range of blood cancers, Syros will evaluate the maximum tolerated dose of SY-5609 in patients with relapsed hematologic malignancies, including B-cell lymphomas, such as mantle cell lymphoma, before starting a focused expansion cohort. The Phase 1 trial is expected to begin in the second half of 2022, with data expected mid-2023, which will inform further development in specific hematologic cancers.

In August 2021, Syros entered into an agreement with Roche to exploreSY-5609 in combination with atezolizumab in patients with BRAF-mutant colorectal cancer (CRC), and Roche plans for this arm of its ongoing Phase 1/1b INTRINSIC trial to be open for enrollment in the first half of this year. Under the terms of this agreement, Roche is the sponsor of the trial and Syros is supplying SY-5609.

Gene Control Discovery Engine

Syros announced today that the next development candidate from its gene control discovery engine will be a CDK12 inhibitor. Syros plans to nominate this candidate in the second half of 2022.

Syros also announced today that small molecule inhibitors of CDK11 and WRN are the focus of two additional oncology programs in discovery.

Financial Guidance

Based on its current operating plans, 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 2023.

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 RARA-positive patients with higher-risk myelodysplastic syndrome and acute myeloid leukemia; 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 and blood cancers. 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 tamibarotene, SY-2101 and SY-5609, the potential for Syros' clinical programs to result in new standards of care, the potential of SY-5609 to address a range of hematologic malignancies and patient populations, the timing of anticipated data readouts from Syros' clinical trials, the timing to initiate the Phase 3 clinical trial of SY-2101 in APL and the trial of SY-5609 in hematologic malignancies, the potential for Syros's product candidates to obtain regulatory approval, the timing of nomination of Syros' next development candidate, and the sufficiency of Syros' capital resources to fund its operating expenses and capital expenditure requirements into 2023. 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, 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; risks described under the caption "Risk Factors" in Syros' Annual Report on Form 10-K for the year ended December 31, 2020 and Quarterly Report on Form10-Q for the quarter ended September 30, 2021, 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.

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