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 8, 2018**

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.)

620 Memorial Drive, Suite 300 **Cambridge, Massachusetts** (Address of Principal Executive Offices)	**02139** (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))

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 1.01 Entry into a Material Definitive Agreement.

Collaboration Agreement

On January 8, 2018, Syros Pharmaceuticals, Inc. (the "**Company**") and Incyte Corporation ("**Incyte**") entered into a Target

Discovery, Research Collaboration and Option Agreement (the "**Collaboration Agreement**"). Under the Collaboration Agreement, the Company will use its proprietary gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte will receive options to obtain exclusive worldwide rights to intellectual property resulting from the collaboration for the development and commercialization of therapeutic products directed to up to seven validated targets. Incyte will have exclusive worldwide rights to develop and commercialize any therapies under the collaboration that modulate those validated targets.

Under the terms of the Collaboration Agreement, Incyte will pay the Company $10.0 million in up-front consideration, consisting of $2.5 million in cash and $7.5 million in pre-paid research funding. The Company's activities under the Collaboration Agreement are subject to a joint research plan and, subject to certain exceptions, Incyte will be responsible for funding the Company's activities under the research plan, including amounts in excess of the pre-paid research funding amount.

The Company will be eligible to receive target selection milestone payments and option exercise fees of up to an aggregate of $54.0 million if Incyte selects the maximum number of targets for validation and exercises its option to obtain exclusive rights to collaboration intellectual property for therapeutic products directed to all seven validated targets. Should any therapeutic product be developed by Incyte against a target as to which Incyte has exercised its option to obtain exclusive rights to collaboration intellectual property, the Company will be eligible to receive milestone payments and, if approved and commercialized, royalty payments from Incyte. For each of the seven validated targets, the Company would become eligible to receive from Incyte a total of up to $50.0 million in development and regulatory milestone payments. If products arising from the collaboration are approved, the Company would become eligible to receive from Incyte, for each validated target, a total of up to $65.0 million in commercial milestone payments. Upon approval and commercialization of any therapeutic product resulting from the collaboration, the Company would become eligible to receive low single-digit royalties on net sales of such product.

The term of Collaboration Agreement begins on January 8, 2018 and, unless terminated by a party early, will continue until all royalty obligations for products arising from the collaboration expire. The Collaboration Agreement may be terminated by Incyte for convenience on sixty (60) days' prior written notice to the Company, or by the Company on thirty (30) days' written notice in the event Incyte or one of its affiliates or sublicensees challenges the validity or enforceability of certain patent rights controlled by the Company. The Collaboration Agreement may also be terminated by either of the parties on thirty (30) days' prior written notice in the event of an uncured material breach of the Collaboration Agreement by the other party or immediately in the case of certain bankruptcy events. Incyte's right to terminate for convenience and each party's right to terminate for uncured material breach may be exercised either with respect to the Collaboration Agreement in its entirety or, as applicable, in relation to the relevant validated target and associated therapeutic products.

The foregoing description of the material terms of the Collaboration Agreement is qualified in its entirety by the terms of the Collaboration Agreement, which the Company intends to file as an exhibit to its Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

Stock Purchase Agreement

In addition, on January 8, 2018, the Company entered into a Stock Purchase Agreement with Incyte (the "**Stock Purchase Agreement**"), pursuant to which Incyte agreed to purchase 793,021 shares of the Company's common stock, par value $0.001 per share (the "**Shares**"), for an aggregate purchase price of $10.0 million in cash, or $12.61 per share, in a private placement. The purchase price represents a thirty percent (30%) premium to the volume-weighted sale price of the shares of the Company's common stock over the fifteen (15) trading day period immediately preceding the date of the Stock Purchase Agreement. The Shares will be subject to a lock-up restriction and a market stand-off agreement for a period of 12 months following the closing of the sale of the Shares (the "**Closing**").

Pursuant to the terms of the Stock Purchase Agreement, the Company has agreed to file a registration statement covering the resale by Incyte of the Shares within 20 days following the Closing. The Company has agreed to use commercially reasonable efforts to cause such registration statement to become effective no later than the last day of the fiscal quarter in which the Shares are delivered to Incyte, and to keep such registration statement effective until the date the Shares covered by such registration statement have been sold or may be sold without volume restrictions pursuant to Rule 144 under the Securities Act of 1933, as amended (the "**Securities Act**"). The Company has agreed to be responsible for all fees and expenses incurred in connection with the registration of the Shares for resale. The Company has granted to Incyte, and Incyte has granted to the Company, customary indemnification rights in connection with the registration statement.

In addition, from the Closing until the earlier of the second anniversary of the Closing or the expiration or termination of the Collaboration Agreement, the Company has granted to Incyte the right to purchase up to its pro rata share of the securities offered in certain subsequent offerings of the Company's common stock or common stock equivalents, subject to the terms and conditions set forth in the Stock Purchase Agreement.

The foregoing description of the material terms of the Stock Purchase Agreement is qualified in its entirety by the terms of the Stock Purchase Agreement, which the Company intends to file as an exhibit to its Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

Item 3.02 Unregistered Sales of Equity Securities.

The information contained above in Item 1.01 is hereby incorporated by reference into this Item 3.02. Based in part upon the representations of Incyte in the Stock Purchase Agreement, the offering and sale of the Shares will be exempt from registration under Section 4(a)(2) of the Securities Act. The Shares will not be registered under the Securities Act or any state securities laws and may not be

offered or sold in the United States absent registration with the Securities and Exchange Commission (the "**SEC**") or an applicable exemption from the registration requirements. The sale of the securities will not involve a public offering. Incyte represented that it is an accredited investor, as such term is defined in Rule 501(a) of Regulation D under the Securities Act, and that it is acquiring the Shares for investment purposes only and not with a view to any distribution of the Shares in violation of the United States federal securities laws.

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 8, 2018, is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

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, as amended (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 or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On January 8, 2018, the Company issued a press release announcing its 2018 business goals and financial guidance. 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.

Forward-Looking Statements

This Form 8-K contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including without limitation statements regarding the Company's business, plans, prospects

and strategies, its plans regarding preclinical and clinical development of its product candidates, its expected financial results, its expectations regarding the Collaboration Agreement with Incyte and its plans to file a registration statement to register the resale of the shares of common stock to be issued and sold to Incyte under the Stock Purchase Agreement. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "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 risks relating to the ability of the parties to successfully research, develop and commercialize products under the Collaboration Agreement; the Company's ability to comply with its obligations under and otherwise maintain the Collaboration Agreement with Incyte on the agreed upon terms; advance the development of its programs, including SY-1425 and SY-1365, under the timelines it projects in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with the *RARA* and *IRF8* biomarkers; 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' Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which is on file with the SEC; and risks described in other filings that Syros makes with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Syros expressly disclaims any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.	Description
99.1	Presentation dated January 8, 2018
99.2	Press release dated January 8, 2018

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 8, 2018

By: /s/ Nancy Simonian
Nancy Simonian, M.D.
President & Chief Executive Officer

Exhibit 99.1

Syros Announces 2018 Strategic Priorities and Expected Milestones

On Track to Report Clinical Data on SY-1425 Combinations and SY-1365

Initial Expansion of Phase 1 Clinical Trial of SY-1365 to Focus on Ovarian Cancer

Company Leverages Gene Control Platform for Target Discovery Collaboration with Incyte

CAMBRIDGE, Mass., January 8, 2018 — Syros Pharmaceuticals (NASDAQ: SYRS), a biopharmaceutical company pioneering the development of medicines to control the expression of genes, today outlined its strategic plan and expected milestones for 2018. In a presentation at the 36th Annual J.P. Morgan Healthcare Conference on Thursday, January 11, 2018, at 10:30 a.m. PST (1:30 p.m. EST), the Company will detail its three strategic priorities for the year:

- Aggressively advancing its two clinical-stage programs with planned data readouts on two combinations with SY-1425, a first-in-class selective retinoic acid receptor alpha (RARa) agonist, from the ongoing Phase 2 trial in genomically defined acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients, and with the first clinical data for SY-1365, a first-in-class selective cyclin-dependent kinase 7 (CDK7) inhibitor, from the Phase 1 trial in advanced solid tumors.
- Leveraging its leading gene control platform to fuel its discovery and preclinical pipeline in oncology, including immuno-oncology, and the recent expansion into monogenic diseases, keeping the Company on track to achieve its goal of delivering one Investigational New Drug (IND) application every other year on average.
- Building on its strong fundamentals to continue its evolution toward a fully integrated biopharmaceutical company with therapies that transform patients' lives.

Syros also announced today that it has entered into a strategic collaboration and option agreement with Incyte Corporation to identify novel targets for myeloproliferative neoplasms (MPNs), a group of blood cancers in which the body makes too many white or red blood cells or platelets. Under the agreement, Syros will use its proprietary gene control platform for target discovery and validation and Incyte will be responsible for drug discovery, development and commercialization. Syros will receive $10 million upfront and a $10 million equity investment at a premium to the current market price. Syros could receive up to $47 million from Incyte in target validation and option exercise fees. Syros could receive up to $115 million in potential development, regulatory and commercial milestone payments per target for up to seven validated targets, plus low single-digit royalties on sales of products that result from the collaboration.

"We have made great strides over the past year, with data validating the ability of our platform to enrich for patients most likely to respond to SY-1425, the advancement of a second program into clinical development, the initiation of our first program in monogenic diseases and a strategic collaboration around our leading gene control platform," said

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Nancy Simonian, M.D., chief executive officer of Syros. "These accomplishments position us for a transformative year in 2018 with the opportunity for multiple clinical data readouts for SY-1425 and SY-1365, a robust and growing discovery and preclinical pipeline and the continued evolution of our team and capabilities. In 2018, we are focused on continuing to execute with excellence as we strive to build a great and sustainable company that translates our leadership in gene control into therapies that provide a profound and durable benefit for patients."

Expected 2018 Milestones

SY-1425

- Report clinical data in second half of 2018 on SY-1425 in combination with azacitidine in biomarker-positive newly diagnosed AML patients who are not suitable candidates for standard chemotherapy.
- Report clinical data in second half of 2018 on SY-1425 in combination with daratumumab in biomarker-positive relapsed or refractory AML and higher-risk MDS patients. Janssen Research and Development, LLC is providing daratumumab for the clinical trial under a clinical supply agreement.

SY-1365

- Report clinical data in second half of 2018 from dose escalation phase of Phase 1 trial in advanced solid tumor patients.
- Open expansion cohorts in ovarian cancer in mid-2018 exploring SY-1365 as a single agent and in combination with carboplatin. Based on robust anti-tumor activity in multiple relapsed and refractory ovarian cancer patient-derived xenograft models, Syros plans to focus the expansion phase of the ongoing Phase 1 clinical trial on ovarian cancer with cohorts evaluating SY-1365 in multiple ovarian cancer populations as a single agent and in combination with carboplatin.

Platform and Early-Stage Pipeline

- Select a new development candidate.
- Advance discovery programs in cancer and sickle cell disease. Syros' drug discovery program in sickle cell disease is the first

under its monogenic disease strategy to target gene regulatory elements to modulate the expression of a single known gene.
- Execute on target discovery work in MPNs in collaboration with Incyte.

Financial Guidance

Based on its current operating plans, Syros expects that its existing cash, cash equivalents and marketable securities, together with the upfront cash and equity investment from its collaboration with Incyte, will enable the Company to fund its anticipated operating expenses and capital expenditure requirements into 2019. Syros had approximately $81.9 million in cash, cash equivalents and marketable securities as of September 30, 2017.

Presentation at 36th Annual J.P. Morgan Healthcare Conference

Syros will webcast its corporate presentation from the 36th Annual J.P. Morgan Healthcare Conference in San Francisco on Thursday, Jan. 11, 2018, at 10:30 a.m. PST (1:30 p.m. EST). A live webcast of the presentation and question and answer session can be accessed under Events & Presentations in the News and Investors section of the Company's website at

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www.syros.com. A downloadable copy of the corporate slide presentation is also available on the News and Investors section of the website. A replay of the webcast will be archived on the website for approximately 30 days following the presentation.

About Syros Pharmaceuticals

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

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including without limitation statements regarding the advancement of the Company's clinical-stage programs, including the reporting of clinical data from the combination cohorts of the ongoing Phase 2 clinical trial of SY-1425 and the dose escalation phase of the SY-1365 clinical trial in the second half of 2018, and the initiation of expansion cohorts of SY-1365 in multiple ovarian cancer populations; the selection of a development candidate for IND-enabling studies during 2018; the advancement of the Company's preclinical programs, including programs in oncology and sickle cell disease; the Company's ability to execute in its target discovery collaboration with Incyte and receive future payments thereunder; the Company's ability to file an IND application every other year on average; the Company's cash runway; and the benefits of Syros' gene control platform. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "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 whether or when Incyte will exercise any of its options or any option exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid, and Syros' ability to: advance the development of its programs, including SY-1425 and SY-1365, under the timelines it projects in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with the *RARA* and *IRF8* biomarkers; 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; the ability of our collaboration partners to satisfy their obligations under our collaboration agreements; manage competition; manage expenses; raise the substantial additional capital needed to

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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' Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which is on file with the Securities and Exchange Commission; and risks described in other filings that Syros makes with the Securities and Exchange Commission in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Syros expressly disclaims any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

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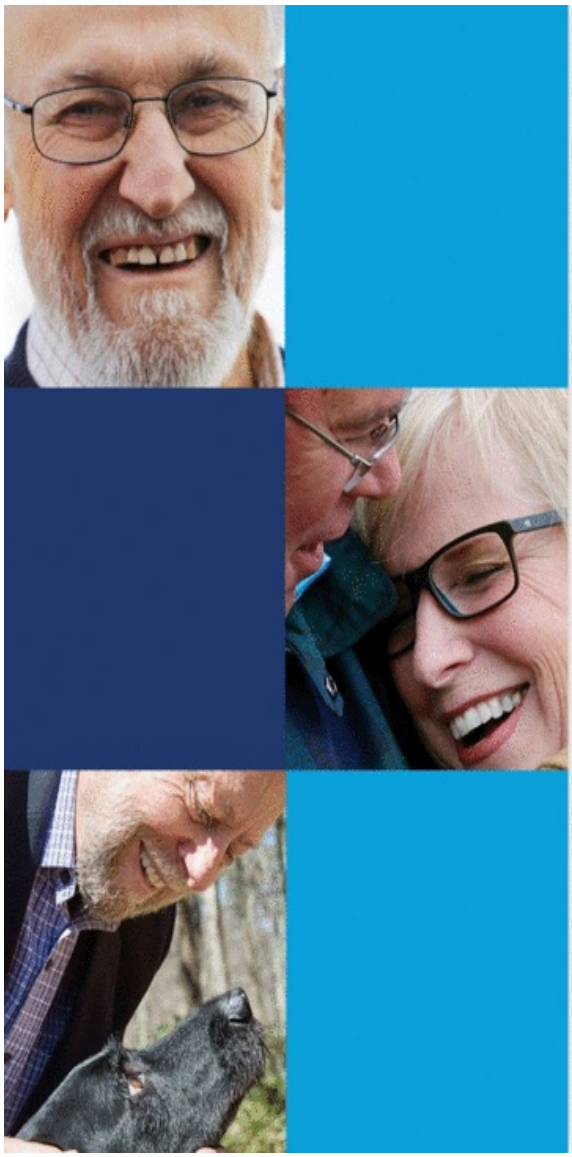
Exhibit 99.2



SYROS

An Expression Makes
a World of Difference

Company Overview

January 2018

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 whether or when Incyte will exercise any of its options or any option exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid, and Syros' ability to: advance the development of its programs, including SY-1425 and SY-1365, under the timelines it projects in current and future clinical trials; advance discovery programs to identify drug candidates for IND-enabling studies; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with *RARA* and *IRF8* biomarkers; 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 our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017 that 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.

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.


Our Vision
To create unparalleled value for patients, employees and shareholders by creating transformative medicines for severe disease through our world-leading expertise in gene control and our exceptional people and culture

Syros

Pioneering	First platform dedicated to the regulatory genome
Rapid translation	2 clinical-stage programs and robust preclinical pipeline in 4 years
Productive	Advancing 1 IND every other year on average
Broad impact	Platform applicable across a wide array of diseases with focus on cancer, I/O and monogenic diseases
Strong foundation	Broad strategic optionality driven by experienced leadership team

Building on our leadership in gene control in 2018

Advance first-in-class clinical programs	Leverage platform to fuel pipeline	Build on fundamentals for evolution toward fully integrated company

2018 objectives and milestones

SY-1425
- Report clinical data on azacitidine and daratumumab combinations in 2H18

SY-1365
- Open Phase 1 expansion in ovarian cancer in mid-2018
- Report clinical data from Phase 1 dose escalation in 2H18

- Select new development candidate
- Advance discovery programs in cancer, immuno-oncology and sickle cell disease
- Execute on target discovery work in MPNs in collaboration with Incyte

- Continue to build out development organization and capabilities
- Maintain financial discipline to execute on top priorities

2017 highlights and recent accomplishments

SY-1425
- Demonstrated single-agent clinical and biological activity in AML and MDS patients
- Demonstrated biologic activity correlated with novel biomarkers

SY-1365
- Initiated Phase1 trial in advanced solid tumors

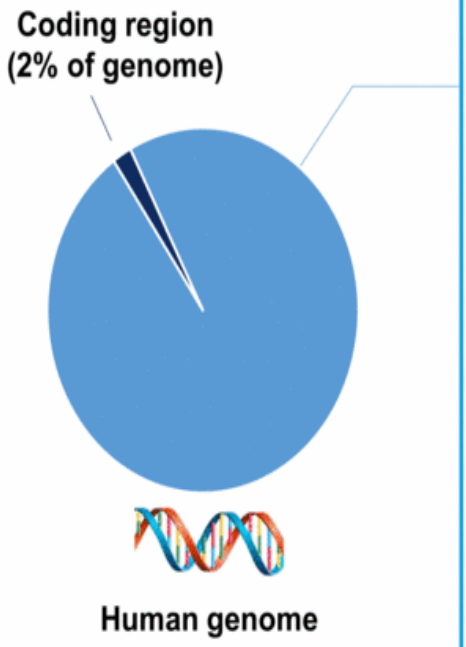
- Advanced preclinical programs towards development candidate
- Initiated monogenic disease program in sickle cell disease
- Established collaboration with Incyte in MPNs

- Brought in $20 million from Incyte collaboration
- Built out team with key BOD additions, newly created CBO role, and development hires
- Maintained financial discipline to execute on top priorities

Gene Control Platform

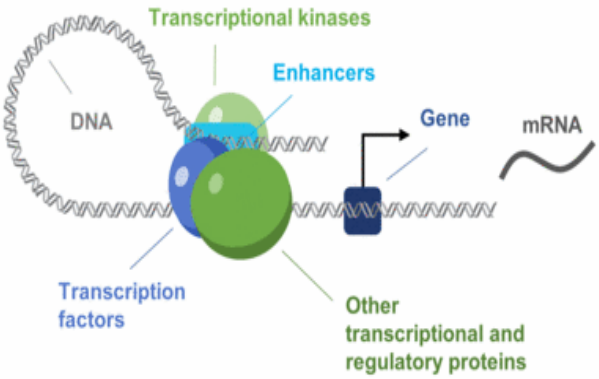
SYROS

Gene expression, controlled by non-coding genome, is central to cell function in health and disease



Non-coding region (98% of genome)

- Controls expression of genes to determine function of all cells
- Alterations involved in wide range of diseases
- Unexploited for drug discovery



Our platform integrates three areas of expertise

Regulatory genomics

- Whole genome analysis to identify dysregulated genes in patient subsets
- Single gene analysis to identify genomic regulatory elements controlling expression of genes
- Gene control biomarkers for patient selection and clinical acceleration

Disease biology

Cancer

- Modulate transcription regulators to drive apoptosis or differentiation

Immuno-oncology

- Modulate tumor cells, macrophages and T cells to promote tumor killing

Monogenic diseases

- Target regulatory elements to modulate expression of known gene

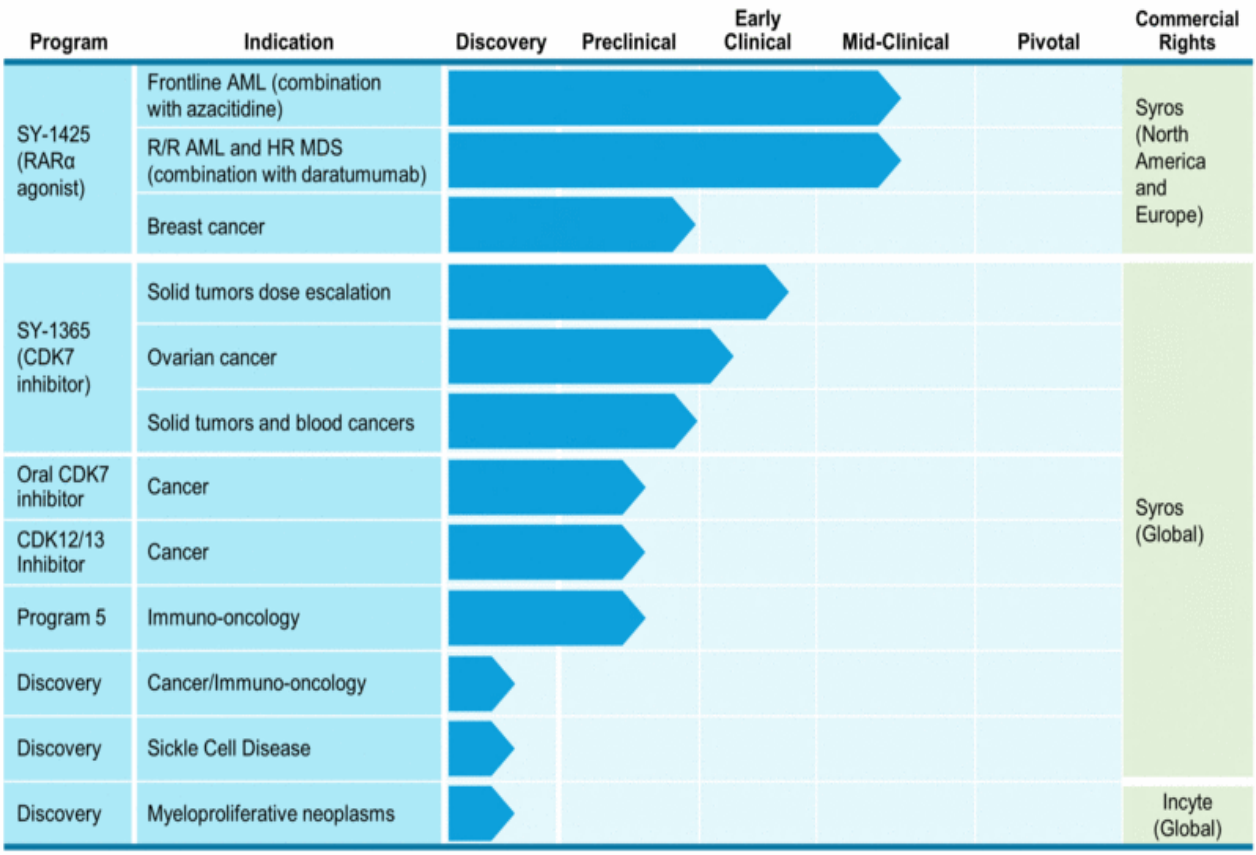
Transcriptional small molecule chemistry

- Biochemical, structural biology and medicinal chemistry expertise in targeting transcription
- Proprietary gene control compound library

Our Programs

SYROS

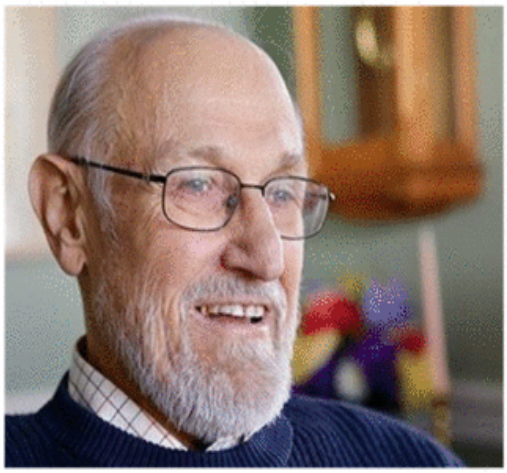
Growing pipeline of multiple first-in-class programs



*SY-1425 is approved in Japan as Amnolake® (tamibarotene) for patients with relapsed/refractory APL

SY-1425 (RARα agonist): Turning on differentiation genes in cancer

Acute Myelogenous Leukemia (AML) and Myelodysplastic Syndromes (MDS)



- First-in-class selective, oral RARα agonist
- Novel AML and MDS subsets and biomarkers discovered by Syros
- In Phase 2 trial in combination with azacitidine and daratumumab
  - Data expected 2H 2018
  - Single-agent activity and myeloid differentiation in biomarker-positive AML and MDS patients support ongoing development in combination
  - Chronic, daily dosing generally well-tolerated
- Significant market potential
  - AML and MDS continue to be areas of high unmet need
  - Few options for newly diagnosed, unfit AML and R/R AML and HR MDS
  - Potential in additional AML and HR MDS subsets and other RARA-positive cancers, including breast

Ongoing Phase 2 trial evaluating SY-1425 combinations in genomically defined AML and MDS patients

- All patients selected based on *RARA* and *IRF8* biomarkers
- Two distinct combinations in difficult-to-treat AML and MDS populations
- Expect to report clinical data on both combinations in second half of 2018

Phase 2 Clinical Trial Design

SY-1425 in combination with azacitidine in newly diagnosed, unfit AML *(25 patients)*

SY-1425 in combination with daratumumab in R/R AML and higher-risk MDS *(12-patient pilot)*

Endpoints

- Overall Response Rate
- Duration of Response
- Hematologic Improvement
- Safety and tolerability
- CD38 induction (daratumumab arm only)

Clinical and biologic activity seen with single agent SY-1425 in difficult to treat AML and HR MDS patients

Phase 2 data showed myeloid differentiation, improved blood counts and reduced bone marrow blasts

- Biomarker status significantly correlated with differentiation of cells treated *ex vivo* with SY-1425, supporting the predictive value of the biomarker test for patient selection
- Clinical activity observed in 43% (10/23) R/R AML and HR MDS and 8% (2/25) LR MDS patients
  - 9 with hematologic improvement
  - 5 with marrow blast reductions, including 1 with marrow CR meeting IWG criteria
- 57% (13/23) R/R AML and HR MDS patients had stable disease
- Myeloid differentiation observed, including induction of CD38 in 85% (11/13) of evaluable patients

Generally well-tolerated with manageable and/or reversible side effects

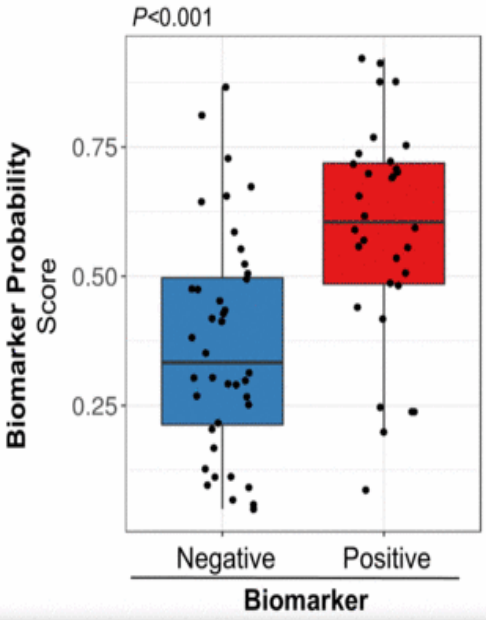
- 58 R/R AML or HR MDS and LR MDS patients treated for median duration of 80 days; patients treated up to 8 months and remaining on study
- Most common AEs consistent with prior experience:
  - Hypertriglyceridemia
  - Fatigue
  - Dermatologic effects
- Majority of AEs were low grade

ASH 59th ASH® Annual Meeting and Exposition Atlanta, GA • December 9-12, 2017

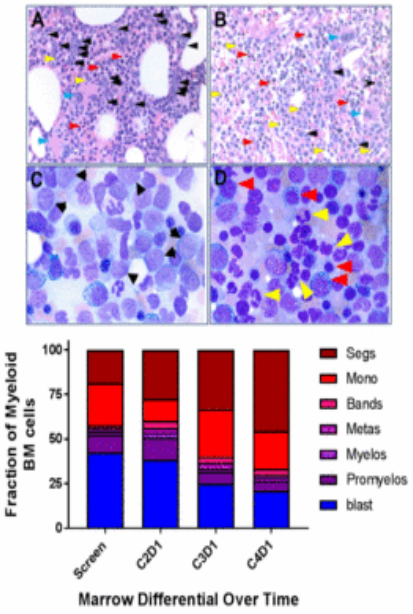
"Early Results from a Biomarker-Directed Phase 2 Trial of SY-1425 in Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Demonstrate DHRS3 Induction and Myeloid Differentiation Following SY-1425 Treatment"

Differentiation observed in biomarker-positive patient samples and clinical trial patients treated with SY-1425

Unbiased machine learning approach using Random-Forest analysis



66-year-old male with R/R AML



Myeloid differentiation starting after one cycle, with marrow blast reduction >25% beginning after two cycles and continuing to the start of the fourth cycle

ESH EUROPEAN SCHOOL OF HAEMATOLOGY

"Novel RARA Pathway Activation Biomarkers in Study SY-1425-201 Define a New Subset of AML and MDS Patients and Correlate with Myeloid Differentiation"

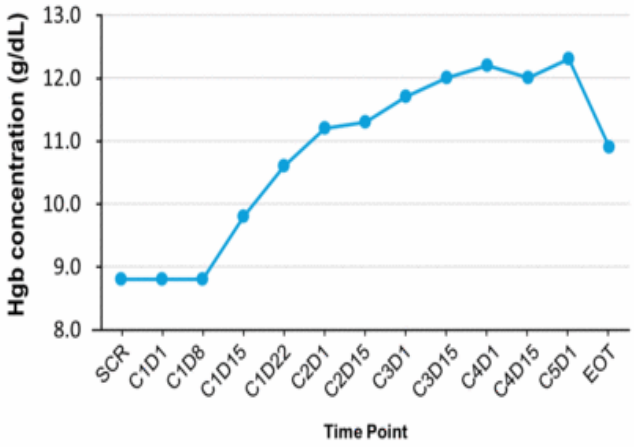
ASH 59th ASH Annual Meeting and Exposition

"Early Results from a Biomarker-Directed Phase 2 Trial of SY-1425 in Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Demonstrate DHRS3 Induction and Myeloid Differentiation Following SY-1425 Treatment"

SYROS

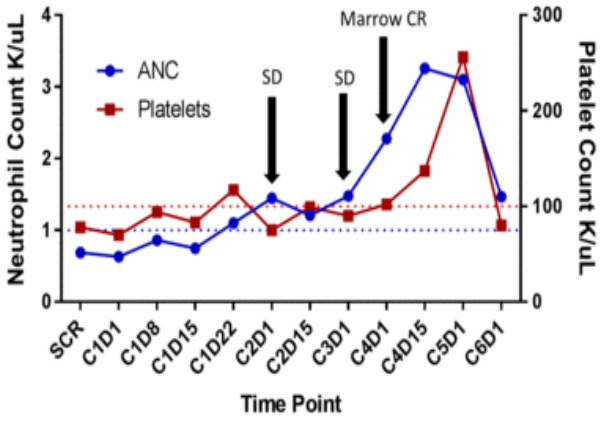
Clinical activity observed in relapsed/refractory patients

Erythroid response in R/R HR MDS patient



Initial response observed two weeks after starting treatment and lasting through five months without blood transfusions

Marrow CR in R/R HR MDS patient



Initial responses (platelet and ANC) observed on cycle 1 day 22, patient remains on treatment past 238 days

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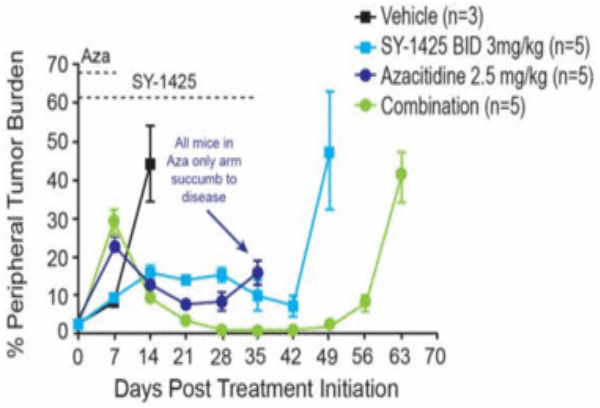
SYROS

SY-1425 and AZA combination induces greater, more durable response than either drug alone and induces apoptosis preclinically

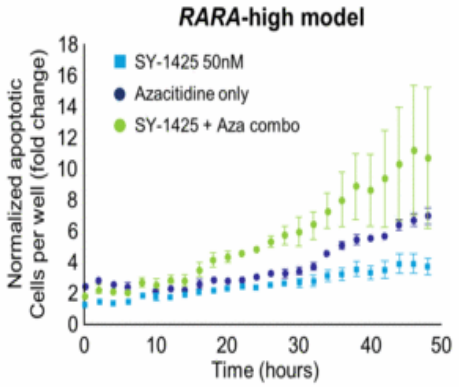
Combo leads to deeper and more durable response in preclinical PDX model

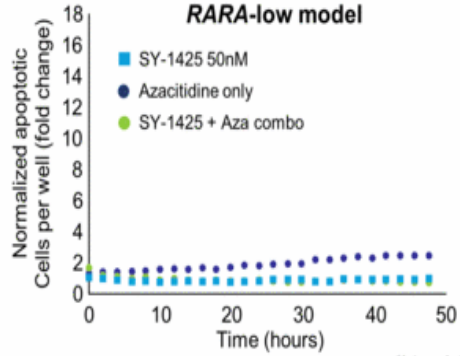


ASH 58th Annual Meeting & Exposition
San Diego, CA • December 3-6, 2016

"Clinical Pharmacodynamic Markers and Combinations with SY-1425 (tamibarotene) in a Genomically-Defined subset of non-APL AML"

Combo induces apoptosis in *RARA*-high cell lines*

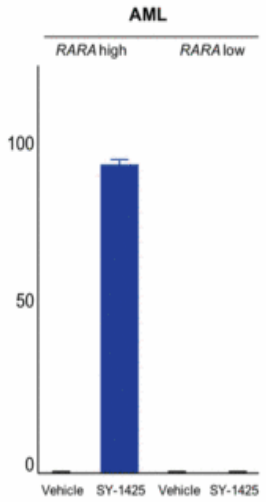




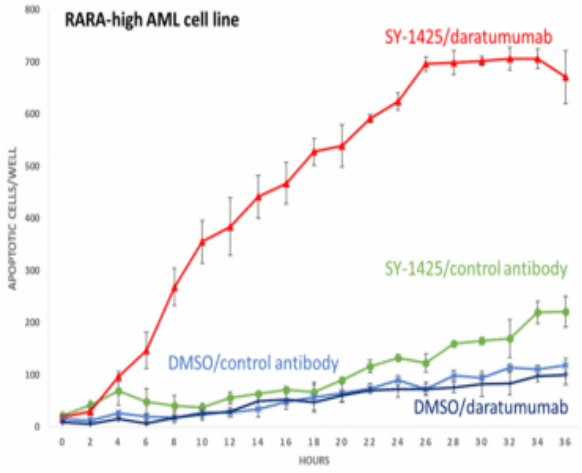
*Internal data on file

SY-1425 induces CD38 expression in preclinical models and patients; Anti-CD38 combination induces immune-mediated cell death *in vitro*

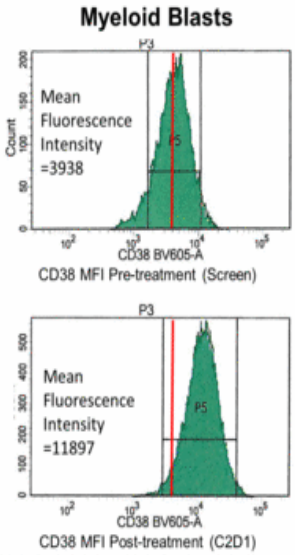
SY-1425 induces CD38 cell surface expression



SY-1425 in combination with daratumumab induces immune-mediated cell death



CD38 induction seen in 85% of evaluable clinical trial patients



AACR American Association for Cancer Research 2017

"SY-1425, a selective RARα agonist, induces high levels of CD38 expression in RARA-high AML tumors creating a susceptibility to anti-CD38 therapeutic antibody treatment"

ASH 59th ASH Annual Meeting and Exposition

"Early Results from a Biomarker-Directed Phase 2 Trial of SY-1425 in Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Demonstrate DHRS3 Induction and Myeloid Differentiation Following SY-1425 Treatment"

SYROS

Significant need for well-tolerated oral therapies that extend survival and improve quality of life

AML incidence[1]: ~33,000

~ 33% *RARA or IRF8* biomarker positive

HR MDS incidence[1]: ~7,500

~ 33% *RARA or IRF8* biomarker positive

Newly diagnosed, unfit

- >50% of AML patients ineligible for standard chemo upon diagnosis
- HMAs/ less intensive therapies with modest efficacy are standard-of-care
- Survival of ≤ 12 months

Newly diagnosed higher-risk

- Most patients treated with HMAs/ less intensive therapies that have modest efficacy
- Survival of 0.8-1.6 years

Relapsed or refractory

- Newly approved agents target limited subsets of patients with modest efficacy
- Patients progress quickly in relapsed setting
- Survival of < 6 months

Relapsed or refractory higher-risk

- Few treatment options with limited efficacy
- No new drugs approved since 2006
- Survival of < 6 months

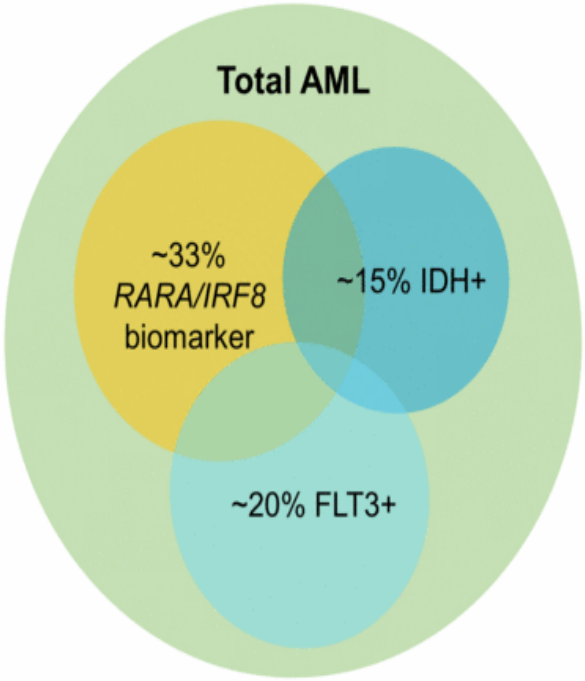
[1] Incidence figures include annual diagnoses in the U.S., Canada and the EU 5 (UK, Germany, France, Spain and Italy). Health Advances analysis.

Sources: Expert Rev. Pharmacoecon. Outcomes Res. Early online, 1–10 (2015); Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 11, 625-36; Blood 2012 120:2454-2465. NCCN Guidelines 2017 MDS.

SYROS

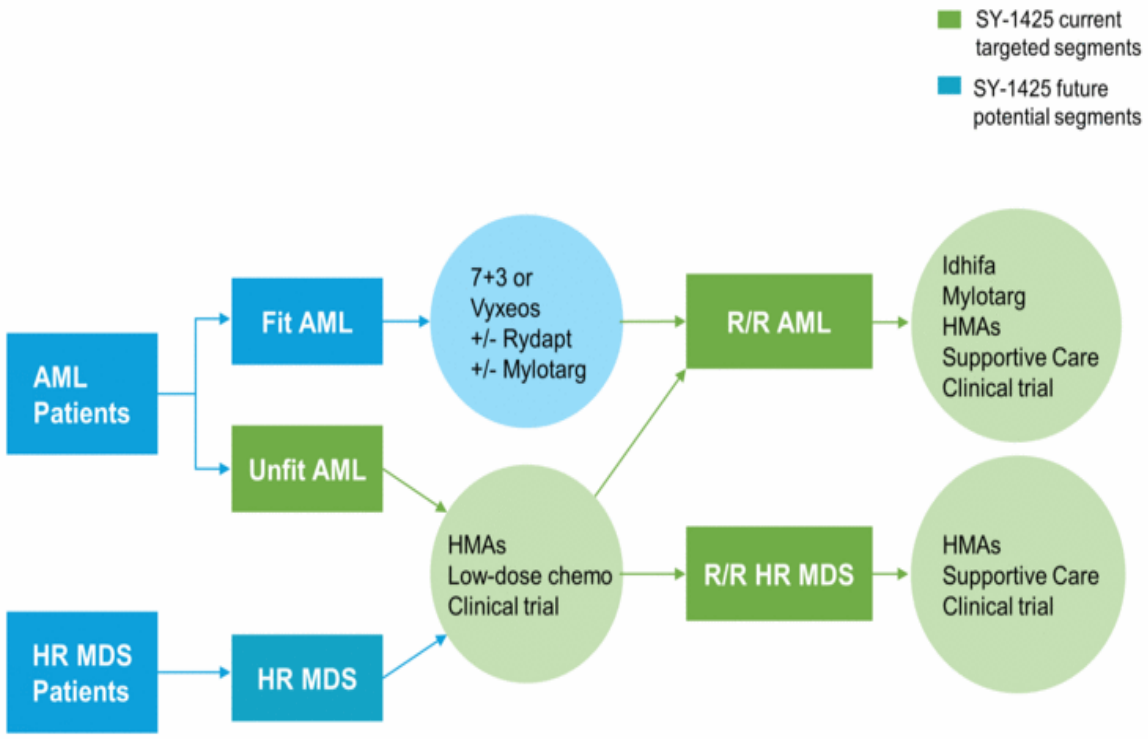
Unique mechanism and tolerability profile support combination potential

- *RARA and IRF8* biomarkers and SY-1425 opportunity cut across mutational landscape
- Unique mechanism points to potential for combinations with chemo and targeted agents without anticipated overlapping toxicities



Estimated frequency of *RARA/IRF8* biomarkers based on Syros' analysis of screed patients in ongoing trial, and estimated frequency of IDH and FLT3 mutations based on published studies

Current and future opportunities for SY-1425 within AML and HR MDS treatment landscape



Source: Health Advances interviews and analysis, SEER 2015, UpToDate 2015, Fernandez HF 2010 ASH, Ohtake S 2004 Blood.

SY-1365 (CDK7 inhibitor): Controlling expression of tumor-driving genes

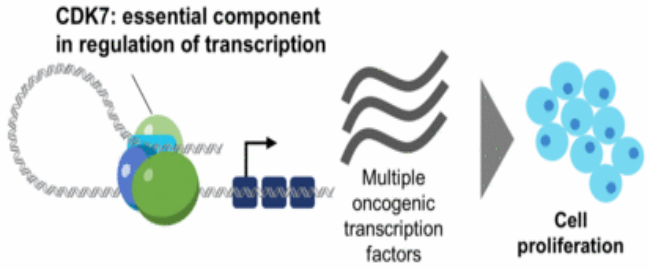
Difficult-to-treat solid tumors and blood cancers

- First-in-class selective inhibitor of CDK7
- Lowers expression of key tumor-driving genes, transcription factors and anti-apoptotic proteins
- CDK7 inhibition induces apoptosis and preferentially kills cancer cells over non-cancerous cells
- Currently in Phase 1 clinical trial with planned expansion into ovarian cancer
  - Data from dose escalation phase expected in second half of 2018
- Broad potential to expand into additional solid tumors and blood cancers

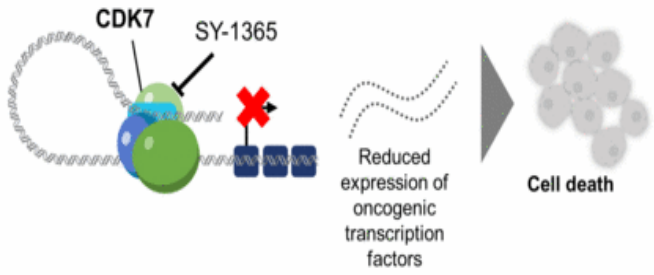
CDK7 inhibition: powerful approach to target transcriptionally driven cancers

Transcriptional addiction: certain cancers become dependent on increased expression of disease-driving transcription factors

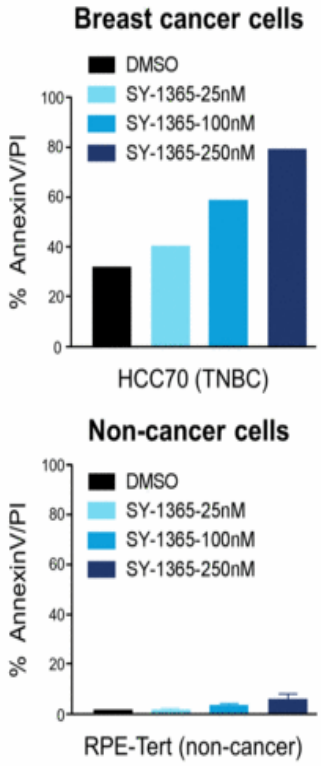
CDK7 is a key player in driving transcription



Inhibiting CDK7 decreases expression of oncogenic TFs



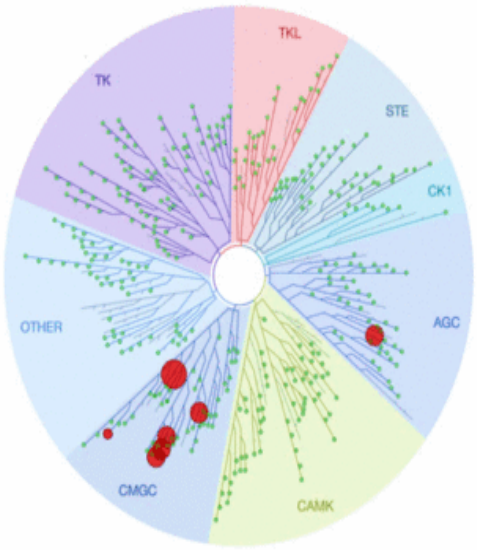
SY-1365 induces apoptosis in cancer cells but not in non-cancer cells



SYROS

SY-1365 is a first-in-class potent and selective CDK7 inhibitor

DiscoveRx kinome scan at 1μM SY-1365



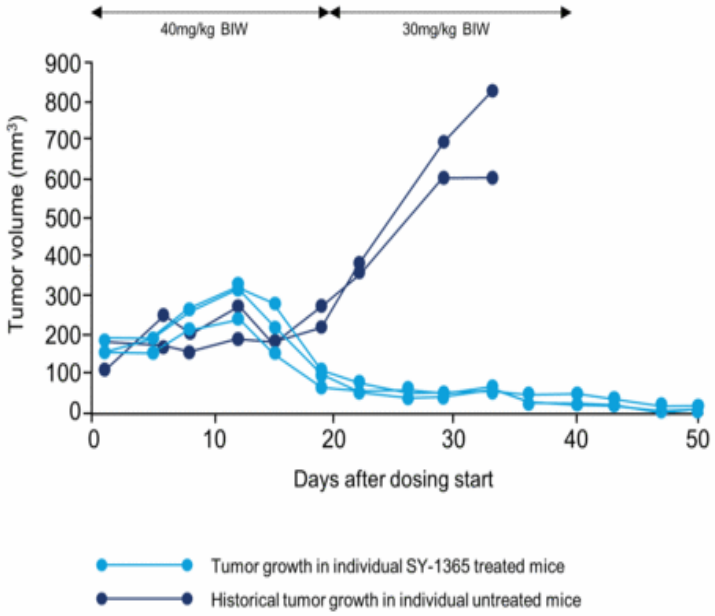
- Covalent
- Highly potent
  - Enzymatic IC50 = 22 nM
  - Cellular IC50 < 20 nM
- Highly selective
  - Greater than 30-fold selective for CDK7 over CDK9 and CDK2
  - Only binds to 7 out of 468 kinases screened at >90% binding
- Sustained PD effect (~3-day half-life)
- Durable tumor regressions in *in vivo* models using intermittent dosing regimen

AACR | NIH National Cancer Institute | EORTC

"PK/PD modeling of the first-in-class, potent and selective covalent CDK7 inhibitor, SY-1365, provides mechanistic basis for intermittent dosing regimens in preclinical efficacy models of hematological and solid tumors"

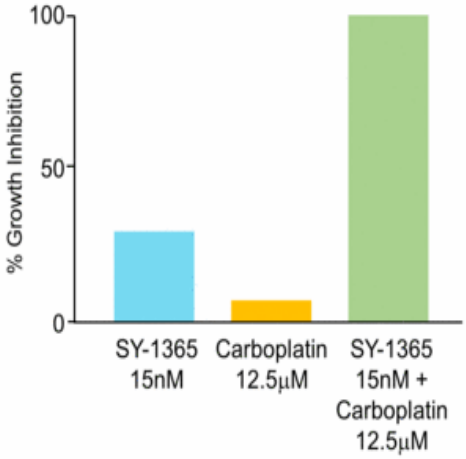
SY-1365 shows anti-tumor activity as single agent and in combination with standard-of-care in ovarian models

Chemo-relapsed ovarian cancer PDX model



Internal data on file

Combination with carboplatin



- Similar combination effect is seen with oxaliplatin and taxol in several ovarian cancer cell lines

Dose escalation ongoing in Phase 1 clinical trial of SY-1365; expansion to initially focus on ovarian cancer (OC)

Phase 1 clinical trial design

Dose escalation
Open to all patients with advanced solid tumors
Exploring once and twice a week dosing

- Relapsed OC, 3+ prior lines
  Single agent (N=24)
- Relapsed OC, 1+ prior lines (platinum sensitive)
  Combination with carboplatin (N=24)
- Primary platinum refractory OC
  Single agent pilot (N=12)
- Solid tumors accessible for biopsy
  Single agent (N=10)

- Expect to present data from dose escalation phase of trial in second half of 2018
  - Safety, PK/PD, proof-of-mechanism
- Expansion phase to focus on ovarian cancer
  - Robust anti-tumor activity in multiple relapsed and refractory ovarian cancer PDX models
  - Focused expansion phase to study multiple OC populations as single agent and in combination
- Sets stage for expansion into additional tumor types

Significant need for therapies that improve survival in advanced high-grade serous ovarian cancer

Ovarian Cancer ~59,000[1]

- 70% have high-grade serous ovarian cancer and most present with advanced disease at initial diagnosis
- Standard-of-care includes platinum-based chemotherapy

Platinum sensitivity is a continuum

Platinum refractory

- 10-15% of patients are refractory to platinum-based therapy at initial treatment
- Progress during or in less than 1 month of completing platinum-based treatment
- Limited treatment options

Platinum resistant

- 30% of patients are resistant to platinum
- Progress within 6 months
- Existing treatment options have limited efficacy with significant toxicities

Platinum sensitive

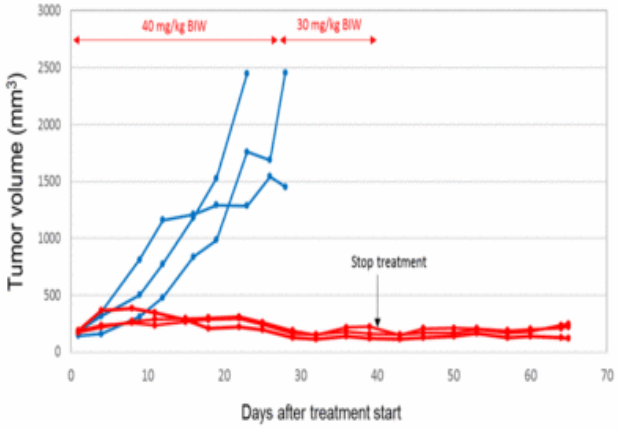
- 55-60% are sensitive or partially sensitive to platinum
- Progress after 6 to 12 months
- Despite initial responses, majority of patients relapse within 3 to 5 years

[1] Incidence figures include annual total ovarian cancer diagnoses, and estimates of high grade serous diagnoses in the U.S., Canada, Japan and the EU 5 (UK, Germany, France, Spain and Italy). Health Advances analysis.

Sources: Hanker et al. Ann Oncol. 2012 Oct;23(10):2605-12. SEER, Cancer Research UK 2013. NCCN Guidelines Nov. 2017. McCluggage WG. Pathology 2011; 43: 420–432. Gabra H. EJC Suppl. 2014 Dec;12(2):2-6. and Herzog TJ and Monk BJ. Gynecol Oncol Res Pract. 2017;4:13.

Preclinical data support potential of SY-1365 as single agent and in combination in additional cancers

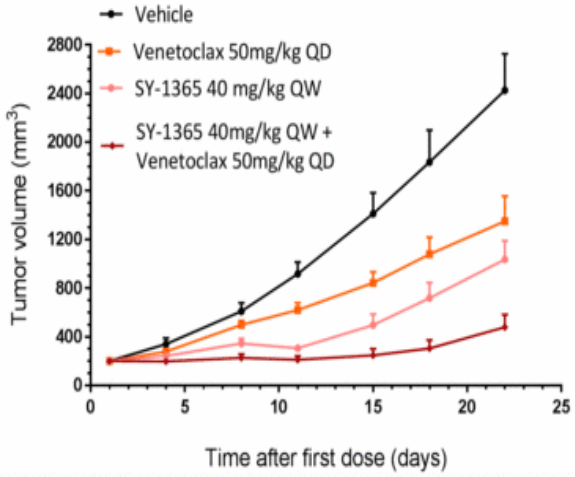
Durable response in PDX models of TNBC



SAN ANTONIO BREAST CANCER SYMPOSIUM

"BCL2L1 (BCLXL) expression and MYC super-enhancer positivity predict sensitivity to the covalent CDK7 inhibitor SY-1365 in Triple Negative Breast Cancer (TNBC) cell lines"

SY-1365 enhances response to venetoclax in CDX model of AML



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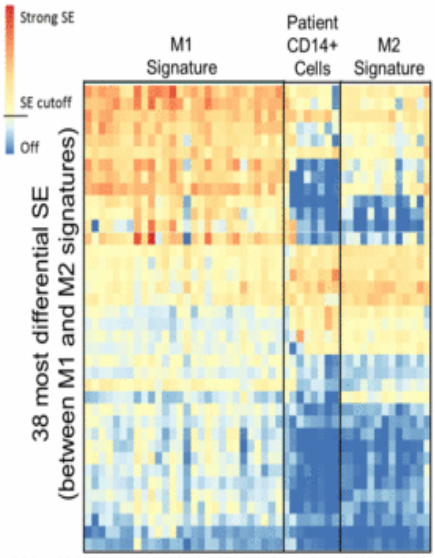
"SY-1365, a potent and selective CDK7 inhibitor, exhibits anti-tumor activity in preclinical models of hematologic malignancies and demonstrates interactions with the BCLXL/BCL2 mitochondrial apoptosis signaling pathway in leukemia"

Immuno-oncology strategy: modulate tumor and immune cells to pro-inflammatory state to promote tumor killing

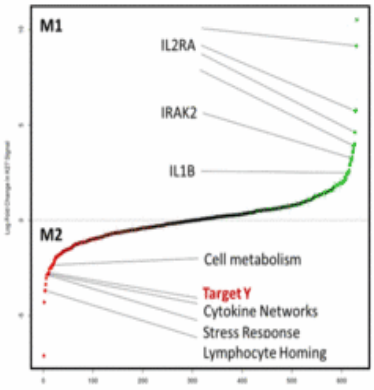
- Analyzed regulatory genomes of tumor and immune cells(breast, ovarian, pancreatic, colorectal, glioblastoma)
- Small molecule inhibitor that switches macrophages to pro-inflammatory state in preclinical studies
- Identified additional targets on tumor and immune cells for modulation

Super-enhancer signatures of M1 and M2 macrophages give insight into the functional state of CD14+ cells



"Characterizing the Epigenetic Landscape Identifies Putative Therapeutic Targets in the Pancreatic Cancer Chimera"

Small molecule inhibitor switches immunosuppressive macrophages to pro-inflammatory state



Immune cell type	Change IFNγ
CD14 naive	--
CD14 naïve*	21x
M1*	61x
M2*	6x
M2 + inhibitor*	61x

*denotes addition of activated CD8 cells

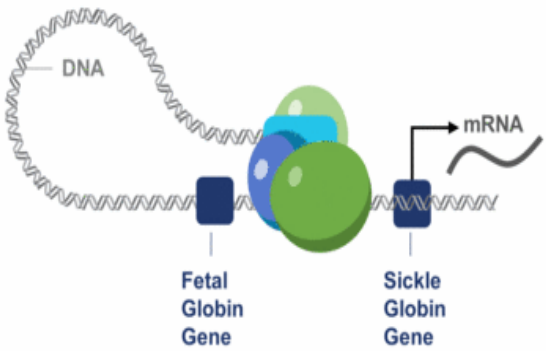
SYROS

Monogenic disease strategy: Target regulatory elements to modulate the expression of a known gene

Sickle Cell Disease (SCD)

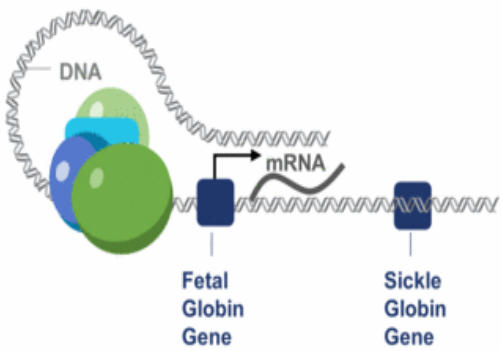
Clinical and genetic data point to therapeutic benefit of elevated fetal globin

- SCD caused by mutated globin gene
- Fetal form typically turned off at birth
- In some SCD patients, the fetal globin gene remains on and is associated with milder disease



Using our platform to develop small molecules to control globin expression

- Developed detailed maps of globin expression in fetal and adult states
- Identifying gene regulatory interactions at the globin locus
- Targeting transcriptional regulators at the globin genes



Company Building

SYROS

Leveraging our platform in collaboration with Incyte to discover novel targets for myeloproliferative neoplasms

- $10 million upfront
- $10 million equity investment
- Up to $47 million in target validation and option exercise fees
- Up to $115 million in development, regulatory and commercialization milestones per target
- Low single-digit royalties on sales of products resulting from the collaboration

- Option to obtain exclusive worldwide rights for up to seven validated targets
- Responsible for drug discovery, development and commercialization
- Exclusive worldwide commercialization rights to any therapies discovered against those validated targets

Pursuing strategic collaborations to maximize potential of our gene control platform

Strategic Collaborations

Platform

- Leverage gene control platform for target and drug discovery collaborations outside our focus areas
- Leverage platform for collaborations within our focus areas where partner's expertise allows us to accelerate or expand our efforts

Programs

- Continue to drive SY-1425 and SY-1365 to key value inflection points
- Assess partnerships post value inflections

In-licensing

- Identify novel genomically defined subsets for patient selection and stratification
- Continue to be opportunistic on drugs that may have activity in our proprietary differential enhancer profiling

Investment balanced across clinical pipeline and discovery to achieve short- and long-term goals

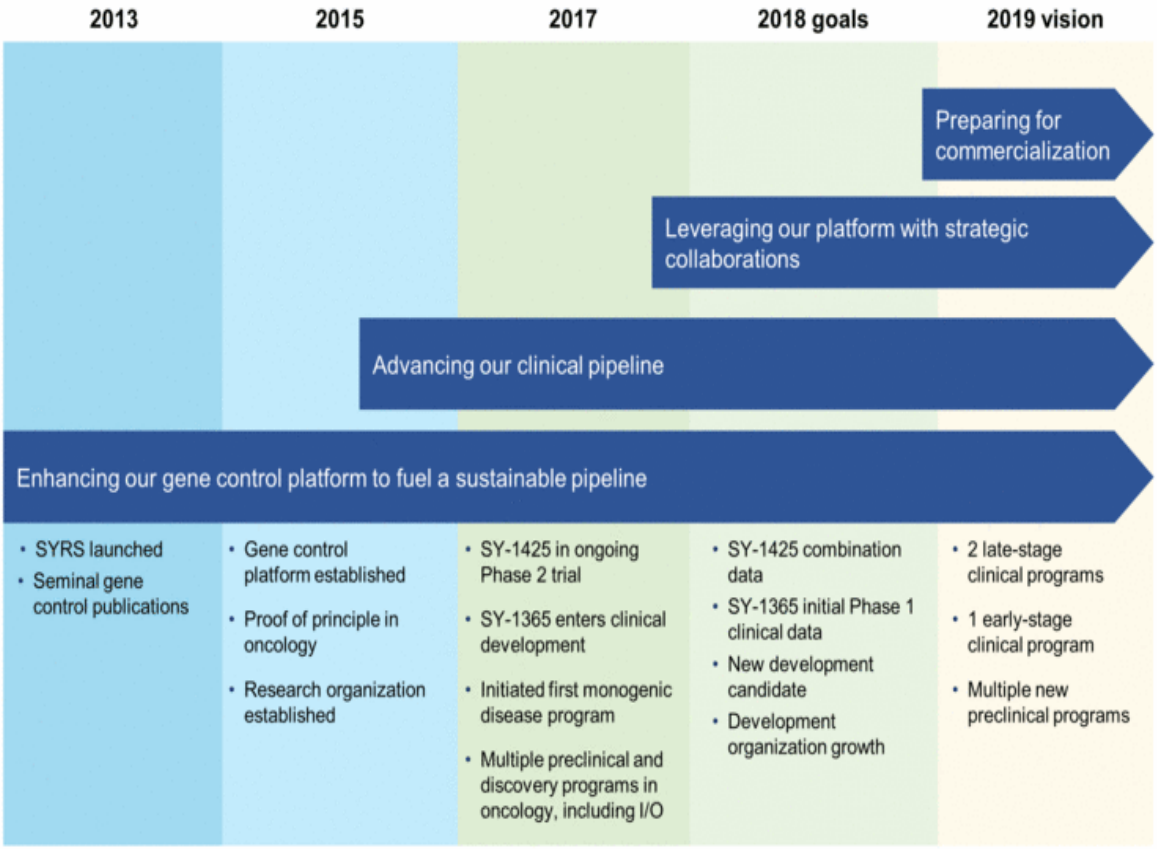
- Drive SY-1425 and SY-1365 to key value creating milestones
- Maintain investment in discovery with goal to:
  - Deliver one IND every other year on average
  - Build on leadership in gene control
- Cash runway into 2019

Cash as of 9/30/2017

~$81.9M

Cash, cash equivalents, marketable securities

Rapidly advancing toward our vision



www.syros.com