
**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): October 17, 2019

Syros Pharmaceuticals, Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware
(State or Other Jurisdiction
of Incorporation)

001-37813
(Commission
File Number)

45-3772460
(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))

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 8.01 Other Events.

On October 17, 2019, Syros Pharmaceuticals, Inc. (the “Company”) issued a press release announcing its decision to prioritize the development of SY-5609 and to discontinue further development of SY-1365. A copy of this press release is filed as Exhibit 99.1 to this Form 8-K and incorporated herein by reference. The information contained on websites referenced in this press release is not incorporated herein.

On October 17, 2019, the Company held a conference call and webcast in which the Company’s management reviewed a slide presentation describing, among other things, data from the expansion portion of the Company’s Phase 1 clinical trial of SY-1365, its intravenous CDK7 inhibitor, and preclinical data from SY-5609, its oral CDK7 inhibitor. This slide presentation is attached as Exhibit 99.2 to this Form 8-K and incorporated herein by reference.

Cautionary Note Regarding Forward-Looking Statements

This Form 8-K 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 Form 8-K, including statements regarding the Company’s strategy, research and clinical development plans, future operations, prospects, plans and objectives of management, are forward-looking statements. 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 the Company’s ability to: advance the development of its programs, including SY-5609, under the timelines it projects; demonstrate in clinical trials the requisite safety, efficacy and combinability of SY-5609; successfully progress SY-5609 through IND-enabling preclinical and toxicology studies; replicate scientific and non-clinical data in clinical trials; obtain and maintain patent protection for SY-5609 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 the Company’s Annual Report on Form 10-K for the year ended December 31, 2018 and Quarterly Report on Form 10-Q for the quarter ended June 30, 2019, each of which is on file with the Securities and Exchange Commission; and risks described in other filings that the Company 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 the Company 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.

<u>Exhibit No.</u>	<u>Description</u>
99.1	Press release dated October 17, 2019
99.2	Slide presentation dated October 17, 2019

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: October 17, 2019

By: /s/ Gerald E. Quirk
Gerald E. Quirk
Chief Legal & Administrative Officer



Syros Announces Update on Selective CDK7 Inhibitor Portfolio

Prioritizing Development of SY-5609, Its Oral CDK7 Inhibitor, and Discontinuing Further Development of SY-1365, Its Intravenous CDK7 Inhibitor

Expects to Initiate Phase 1 Trial of SY-5609 in First Quarter of 2020

Management to Host Conference Call at 8:30 a.m. ET Today

CAMBRIDGE, Mass., October 17, 2019 – Syros Pharmaceuticals (NASDAQ:SYRS), a leader in the development of medicines that control the expression of genes, today provided an update on its portfolio of selective cyclin-dependent kinase 7 (CDK7) inhibitors. The Company has decided to prioritize the development of its highly selective and potent oral CDK7 inhibitor, SY-5609, and to discontinue further development of SY-1365, its intravenous (IV) CDK7 inhibitor. Syros expects to initiate a Phase 1 clinical trial of SY-5609 in patients with select solid tumors in the first quarter of 2020.

SY-5609 inhibits CDK7 more selectively and potently than SY-1365 and has demonstrated greater anti-tumor activity than SY-1365 in multiple preclinical models. Furthermore, initial clinical activity and tolerability data from the expansion of the Phase 1 trial of SY-1365 did not support an optimal profile for patients, particularly in light of an increasing focus on oral targeted agents in cancer. As an oral molecule, Syros believes SY-5609 provides more flexibility in dosing and greater opportunity to sustain the levels of target coverage needed to improve treatment outcomes. Based on these factors, Syros has made a CDK7 portfolio decision to focus on SY-5609.

“We believe in selective CDK7 inhibition as a potentially transformative targeted approach for difficult-to-treat cancers,” said Nancy Simonian, M.D., Chief Executive Officer of Syros. “SY-1365 was the first selective CDK7 inhibitor to enter clinical development, demonstrating proof-of-mechanism for this novel therapeutic approach and showing early signs of clinical activity. We have gained important insights from our work on SY-1365 that have informed our development strategy for SY-5609, including focusing on patient populations most likely to respond to a CDK7 inhibitor. We are prioritizing SY-5609 because we believe it has best-in-class potential and that it provides the greatest opportunity to realize the promise of selective CDK7 inhibition for patients.”

SY-5609: An Oral, Highly Selective and Potent Non-Covalent CDK7 Inhibitor

SY-5609 has induced deep and sustained tumor growth inhibition, including complete regressions, in preclinical models of breast, ovarian and lung cancers at doses below the maximum tolerated dose. SY-5609 has also shown substantial anti-tumor activity in combination with fulvestrant in hormone receptor (HR)-positive breast cancer models that are resistant to CDK4/6 inhibitors. Importantly, SY-5609 showed greater tumor growth inhibition than SY-1365 in preclinical models in which they were both studied, including those that were not responsive to SY-1365.

Syros is on track to complete investigational new drug application-enabling studies for SY-5609 by year-end. The Company expects to initiate a Phase 1 trial in patients with select solid tumors, including breast, lung and ovarian cancers and cancers of any histology defined by a specific molecular signature, in the first quarter of 2020. Syros plans to present new preclinical data on the pharmacokinetics, pharmacodynamics and anti-tumor activity of SY-5609 on October 29 at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston. The abstract for the presentation is available on the conference website at: <https://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=184>.

Initial data from expansion portion of Phase 1 trial of SY-1365

As of a planned September 30 data snapshot, 68 patients had been treated in the expansion portion of the Phase 1 trial of SY-1365, including 53 across the single-agent cohorts in patients with high-grade serous ovarian cancer (HGSOC), relapsed clear cell ovarian cancer and solid tumors of any histology available for biopsy, and 15 patients in the combination cohorts in HGSOC and metastatic CDK4/6 inhibitor-resistant HR-positive breast cancer.

Syros initiated the single-agent expansion cohorts at a dose of 80 mg/m² twice weekly and the combination cohorts at 53 mg/m² once weekly. During the expansion, peri-infusional adverse events (AEs) thought to be related to the IV administration of SY-1365 prompted evaluations of lower doses in the single-agent cohorts and extended infusion times across all the cohorts. Extended infusion times reduced peak drug concentrations and appeared to reduce the overall frequency and severity of peri-infusional AEs, including headache, nausea and vomiting.

The best response observed across the expansion cohorts was stable disease, as defined by RECIST criteria. Response-evaluable patients were primarily treated at doses of 53 and 64 mg/m². Of the 31 response-evaluable patients treated with single-agent SY-1365, 13 (42 percent) had stable disease. Of the 11 response-evaluable patients treated in the combination cohorts, seven (64 percent) had stable disease.

Based on preclinical and clinical data, Syros believes that sustaining the level of CDK7 target coverage needed to enhance clinical activity would require more frequent dosing, or a higher dose that would necessitate further lengthening the infusion to manage tolerability. Syros believes that either approach could create an overly burdensome dosing schedule for patients that can better be addressed with SY-5609.

Conference Call and Webcast:

Syros will host a conference call at 8:30 a.m. ET today to discuss this update on its CDK7 franchise and plans to prioritize the development of SY-5609.

To access the live call, please dial 866-595-4538 (domestic) or 636-812-6496 (international) and refer to conference ID 4578949. A webcast of the call will also be available on the Investors & Media section of the Syros website at www.syros.com. An archived replay will be available for approximately 30 days following the call.

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. Currently focused on cancer and monogenic diseases, Syros is advancing a robust pipeline of development candidates, including SY-1425, a first-in-class oral selective RAR α agonist in a Phase 2 trial in a genomically defined subset of acute myeloid leukemia patients, and SY-5609, a highly selective and potent oral CDK7 inhibitor in investigational new drug application-enabling studies in cancer. Syros also has multiple preclinical and discovery programs in oncology and sickle cell disease. 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' ability to complete IND-enabling preclinical studies by year-end and begin clinical development of SY-5609, including its plans to initiate a Phase 1 clinical trial of SY-5609 in the first quarter of 2020; the reporting of new preclinical data for SY-5609 at the AACR-NCI-EORTC meeting; the potential of SY-5609 to be a best-in-class CDK7 inhibitor; and Syros' ability to replicate preclinical data with SY-5609 in clinical studies; and the potential for selective CDK7 inhibition to be a transformative targeted approach for difficult-to-treat cancers. 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 SY-5609, under the timelines it projects; demonstrate in clinical trials the requisite safety, efficacy and combinability of SY-5609; successfully progress SY-5609 through IND-enabling preclinical and toxicology studies; replicate scientific and non-clinical data in clinical trials; obtain and maintain patent protection for SY-5609 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, 2018 and Quarterly Report on Form 10-Q for the quarter ended June 30, 2019, 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. 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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SYR:OS

An Expression Makes a
World of Difference

CDK7 Portfolio Update
October 17, 2019



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 SY-5609, under the timelines we project; demonstrate in any clinical trials the requisite safety, efficacy and combinability of SY-5609; successfully progress SY-5609 through IND-enabling preclinical and toxicology studies by year-end and initiate clinical development in the first quarter of 2020; replicate scientific and non-clinical data in clinical trials; successfully demonstrate that SY-5609 is a best-in-class CDK7 inhibitor; or that selective CDK7 inhibition can address difficult-to-treat cancers; obtain and maintain patent protection for SY-5609 and the freedom to operate under third party intellectual property; avail ourselves of accelerated regulatory pathways or 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 our business objectives; attract and retain qualified personnel; and successfully execute on our business strategies and long-term vision; risks described under the caption "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2018 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2019, 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.

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.

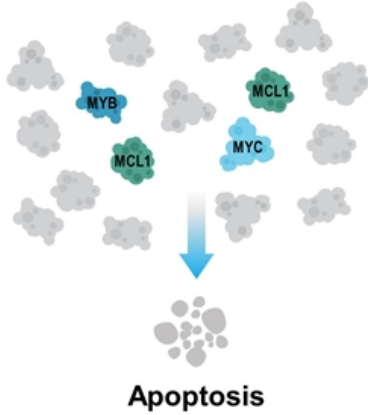
Update on our selective CDK7 inhibitor portfolio

- Portfolio decision to prioritize SY-5609 and discontinue further development of SY-1365 based on a combination of factors, including:
 - Superior preclinical profile of SY-5609, with best-in-class potential in emerging landscape of oral CDK7 inhibitors
 - Initial clinical activity and tolerability data from the expansion that, despite showing some clinical activity, did not support an optimal profile of SY-1365 for patients
- As an oral molecule, we believe SY-5609 provides greater flexibility in dosing and greater opportunity to sustain CDK7 target coverage needed to improve treatment outcomes
- Based on these factors, we believe SY-5609 provides the best opportunity to realize the promise of selective CDK7 inhibition for patients

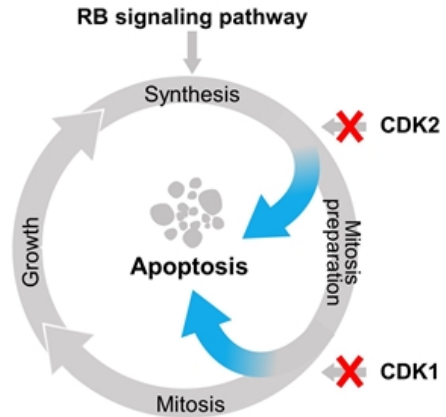
Selective CDK7 inhibition is a potentially transformative targeted approach for difficult-to-treat cancers

Transcription CDK7 Cell cycle

Selectively inhibiting CDK7 has been shown preclinically to decrease expression of oncogenic transcription factors and anti-apoptotic proteins



Selectively inhibiting CDK7 is thought to interfere with cancer-driving adaptations at multiple points in the cell cycle, promoting the induction of apoptosis



Phase 1 clinical trial of SY-1365

Dose escalation

Presented in November 2018 at EORTC-NCI-AACR

- Open to all patients with advanced solid tumors
- Explored once and twice-a-week dosing
- Established proof-of-mechanism with early evidence of clinical activity, including a durable PR at dose of 80 mg/m² and stable disease
- AEs were generally low-grade, including peri-infusional AEs, manageable and reversible

Expansion

Initiated at 53 mg/m² in combination and 80 mg/m² as single agent

Relapsed ovarian cancer, 3+ prior lines
Single agent

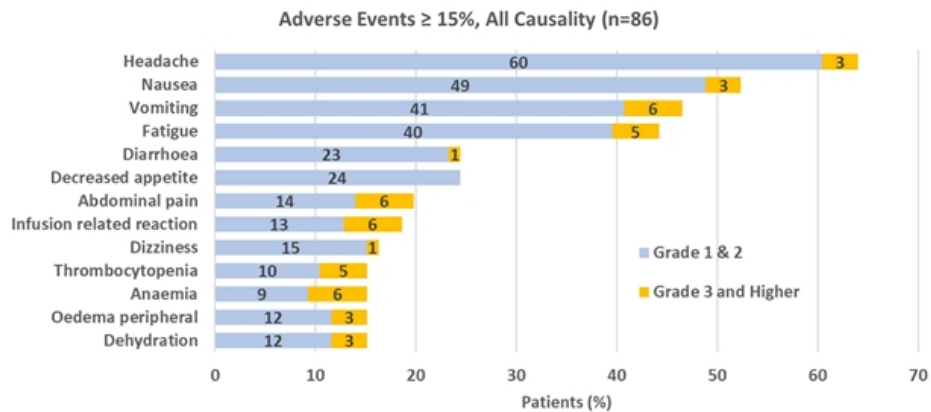
Relapsed ovarian cancer, 1+ prior lines (platinum sensitive)
Combination with carboplatin

Relapsed clear cell ovarian cancer
Single agent

HR+ metastatic breast cancer, CDK4/6 inhibitor resistant
Combination with fulvestrant

Solid tumors accessible for biopsy
Single agent

Overview of single-agent safety data from dose escalation and expansion



- Majority of AEs were low-grade and reversible
- Most frequent AEs occurred on the day of infusion and are thought to be related to IV administration
 - These peri-infusional AEs contributed to early discontinuations
- Lengthening infusion times reduced peak drug concentrations and appeared to reduce frequency and severity of peri-infusional AEs

SY-1365 overview of clinical response in expansion portion of Phase 1 trial

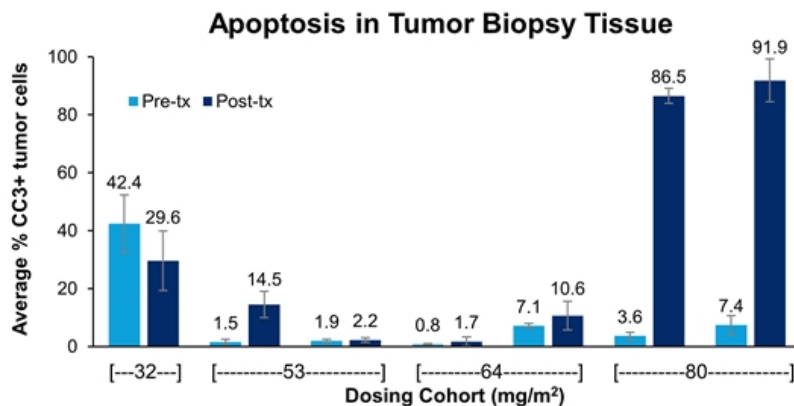
	Patients Treated N	Response-Evaluable Population N	Best Response N (%)
Single Agent	53	31 (HGSOC 13; OCC 1; Biopsy 17)	Stable Disease: 13 (42%)
Combination	15	11 (Carboplatin 8; Fulvestrant 3)	Stable Disease: 7 (64%)

- Majority of response-evaluable patients were treated at 53 and 64 mg/m²
- Best response observed was stable disease
 - Up to 214 days in the single agent setting
 - Up to 337 days in the carboplatin combination



Data as of planned Sept. 30, 2019 data snapshot

Apoptosis observed in tumor tissue in patients treated with SY-1365



- Increases were observed in patients enrolled at doses of 53 mg/m² and higher, with the highest increases observed in both patients enrolled at 80 mg/m²
 - One of the two patients enrolled at 80 mg/m² is the previously reported durable PR from the dose escalation

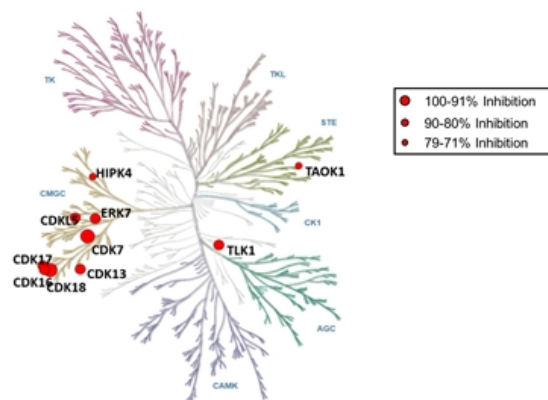
SY-1365 summary

- Proof-of-mechanism established with early evidence of clinical activity
- Majority of AEs thought to be related to IV administration
- Based on preclinical and clinical data, we believe that:
 - Sustained CDK7 target coverage is needed to enhance clinical activity
 - Achieving sustained target coverage with an IV while managing tolerability would create an overly burdensome dosing schedule for patients
 - These challenges can be better addressed with SY-5609

SY-5609 is a superior development candidate, with best-in-class potential

	SY-1365	SY-5609
First-in-class	✓	
Convenience		✓
Potency		✓
Selectivity		✓
Dosing flexibility		✓
Preclinical anti-tumor activity		✓

SY-5609: A highly selective and potent non-covalent oral CDK7 inhibitor



- Only 4 of 485 kinases inhibited at $\geq 90\%$ at 1 μ M
- 13,000- to 49,000-fold more selective for CDK7 over CDK2, CDK9 and CDK12

SY-5609 is more selective and potent than SY-1365

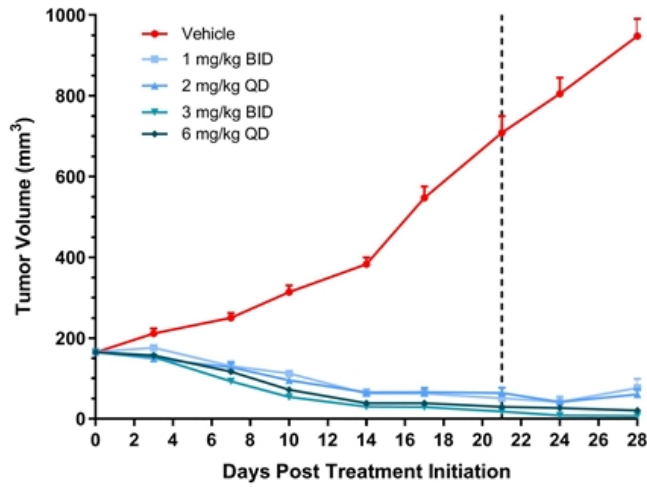
	SY-5609	SY-1365
CDK7 potency	$K_d = 0.059$ nM	$K_i = 20$ nM
CDK12 (fold)	13,000x	5x
CDK2 (fold)	49,000x	53x
CDK9 (fold)	16,000x	23x



Data presented in April 2019 at AACR Annual Meeting

SY-5609 shows tumor growth inhibition, including regressions, below MTD

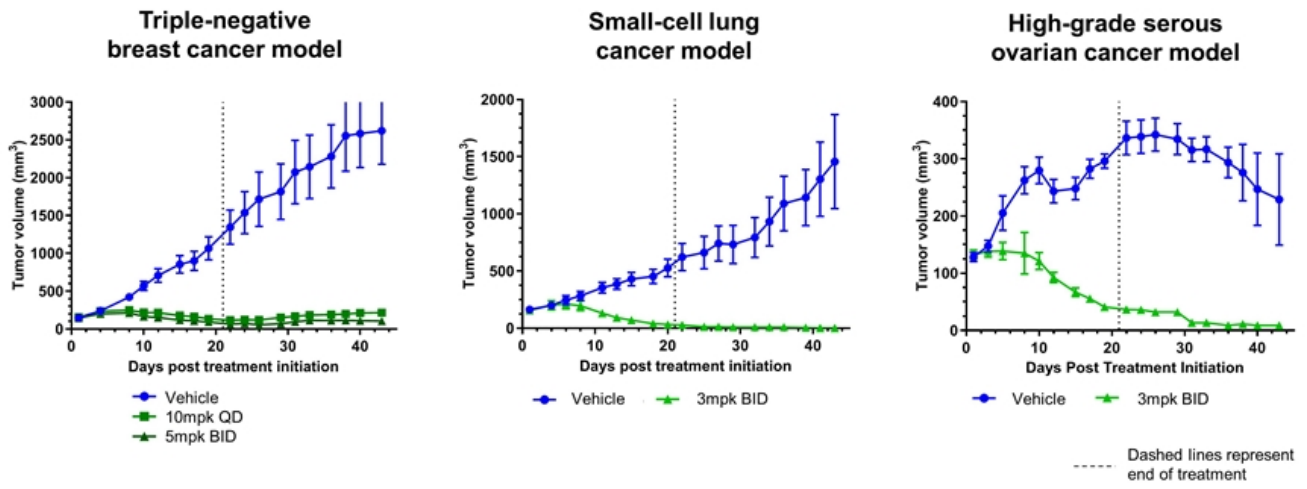
Triple negative breast cancer model



- Regressions observed at 5-fold below MTD of ≥ 10 mg/kg QD

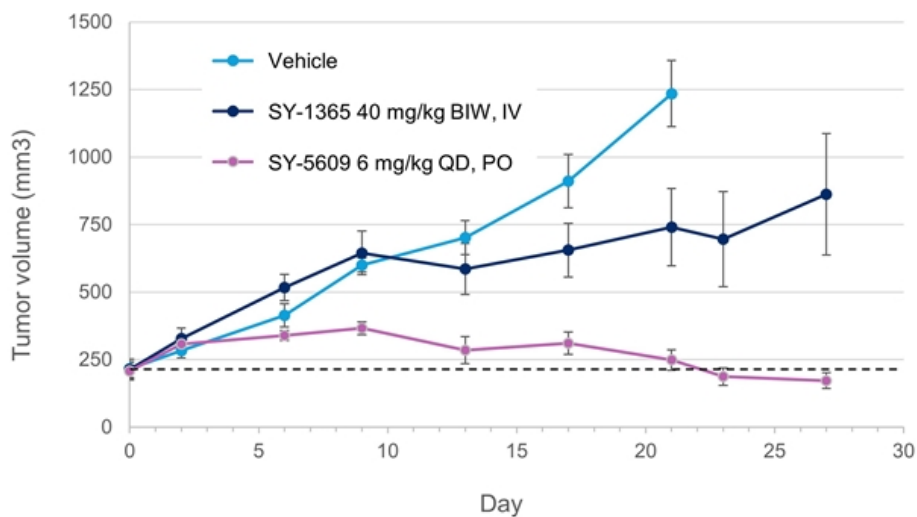
----- Dashed lines represent end of treatment

SY-5609 shows robust anti-tumor activity, including complete regressions, in multiple PDX models



SY-5609 shows greater anti-tumor activity than SY-5609 in head-to-head preclinical study

Pancreatic cancer PDX model



- SY-5609 induces 100% tumor growth inhibition at doses below MTD
- By comparison, SY-1365 induces modest tumor growth inhibition at MTD

Expect to initiate Phase 1 trial in select solid tumors in Q1 2020

- On track to complete IND-enabling studies by year-end
- Dose escalation will enroll patients with select solid tumors
- Focusing on patient populations we believe are enriched for response, including:
 - Breast
 - Lung
 - Ovarian
 - Solid tumors of any histology defined by a specific molecular signature

Key takeaways

- Selective CDK7 inhibition is a potentially transformative targeted approach for difficult-to-treat cancers
- SY-1365 demonstrated early evidence of clinical activity and we believe more sustained CDK7 target coverage is needed to improve treatment outcomes
- SY-5609 is a superior development candidate with best-in-class potential
 - Oral allows dosing flexibility with potential for sustained target coverage and improved tolerability
- Prioritizing SY-5609 allows us to focus where we believe we have the greatest opportunity to deliver on the promise of CDK7 inhibition for patients
- We expect to initiate a Phase 1 trial in Q1 2020 in patients with select solid tumors, including breast, lung and ovarian cancers and cancers with a specific molecular signature

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