An Expression Makes a World of Difference

April 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.

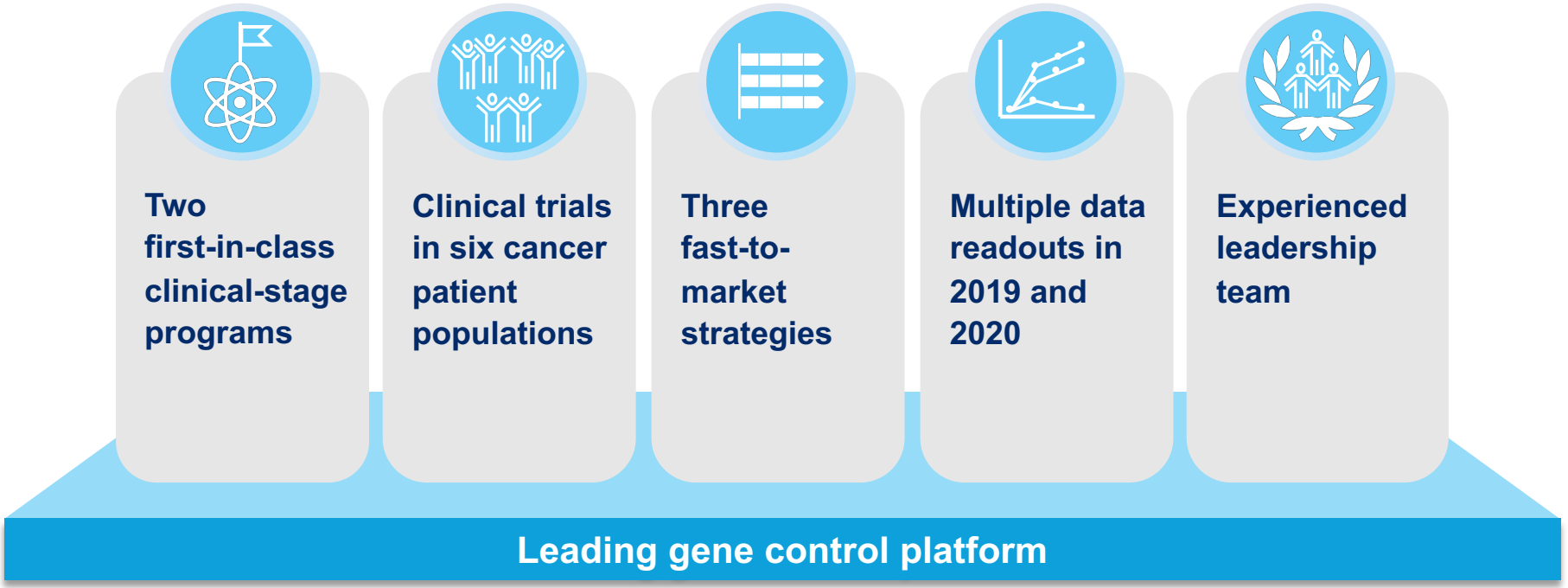
We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including 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, our ability to: advance the development of our programs, including SY-1425 and SY-1365, under the timelines we project in current and future clinical trials or to achieve clinical proof of concept in these trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of our drug candidates; successfully progress SY-5609 through IND-enabling preclinical and toxicology studies; 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 our drug candidates 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, including our ability to perform under the collaboration agreement with Incyte; 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 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

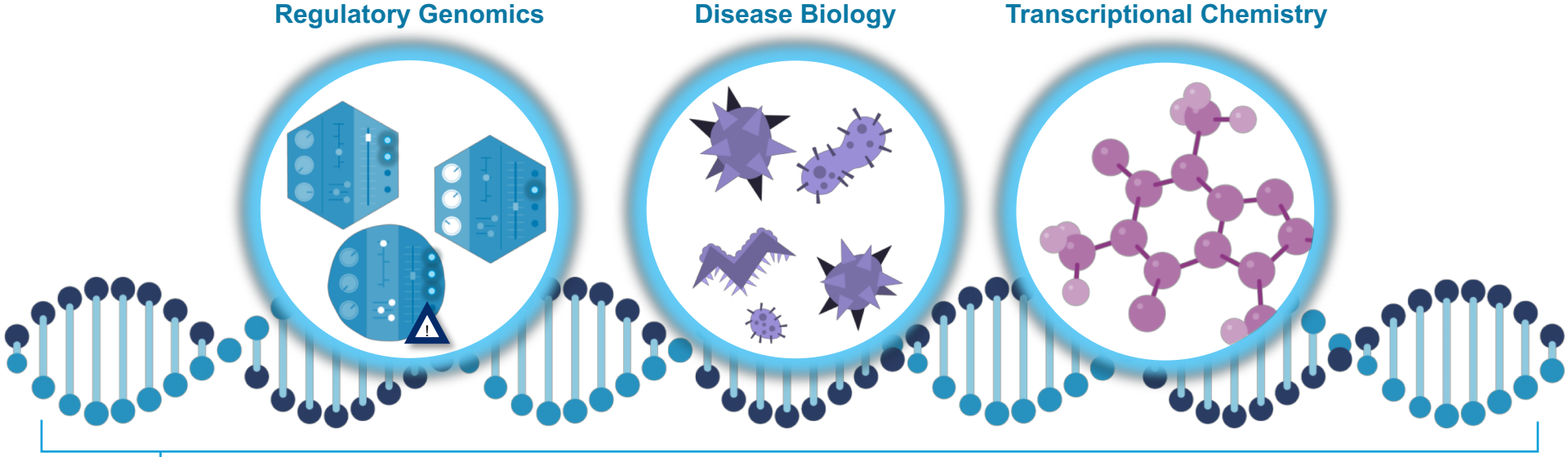
To create unparalleled value for patients, employees and shareholders by creating transformative medicines for severe disease through our world-leading expertise in gene control and our exceptional people and culture

Syros today: Clear vision, growing pipeline, pioneering platform



Pioneering a new approach: Medicines that control the expression of genes

Our leading gene control platform

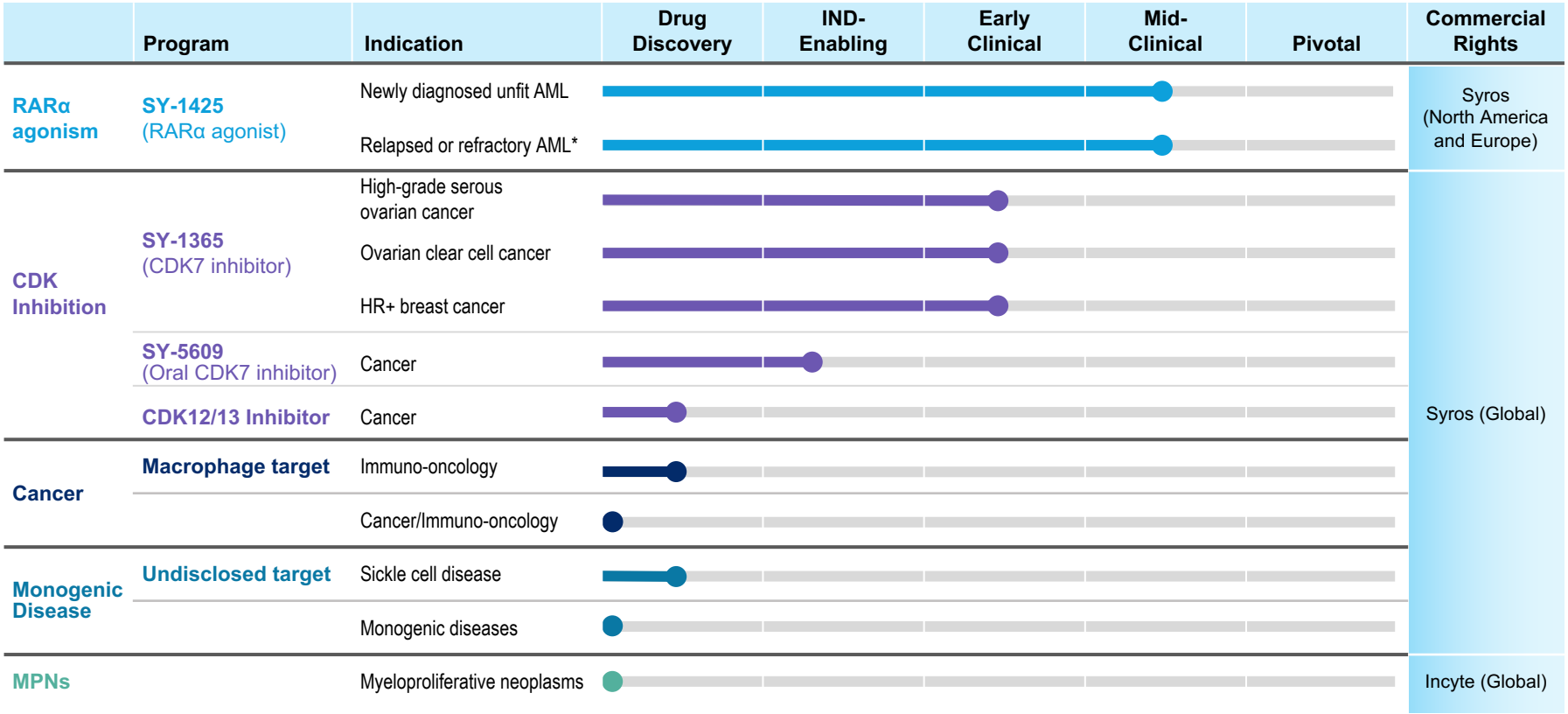


98% Previously unexplored regulatory regions of the genome control the expression of genes determining cell function; majority of disease variation found in these regions

Patient Impact

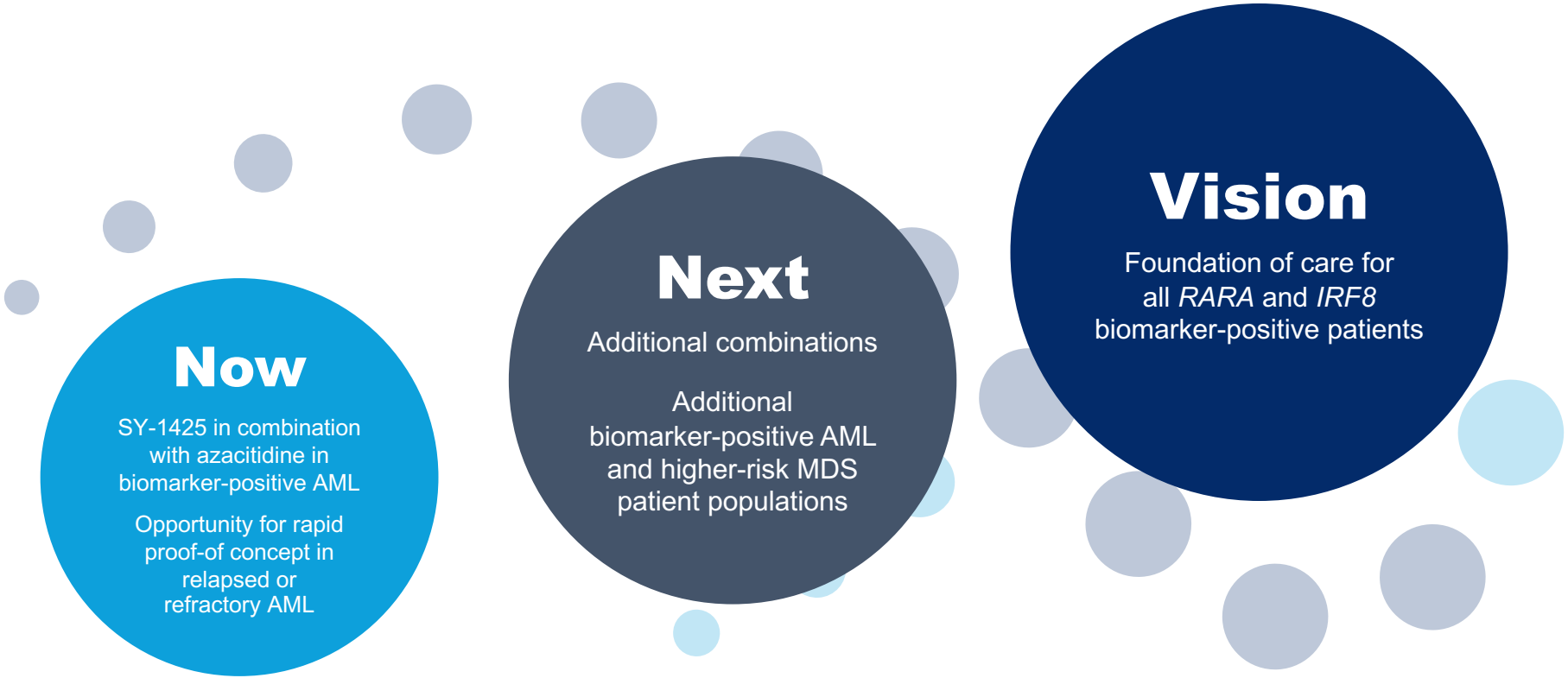
Medicines that control the expression of genes to provide a profound benefit for patients with severe diseases

Deep and growing pipeline with multiple potential first-in-class programs



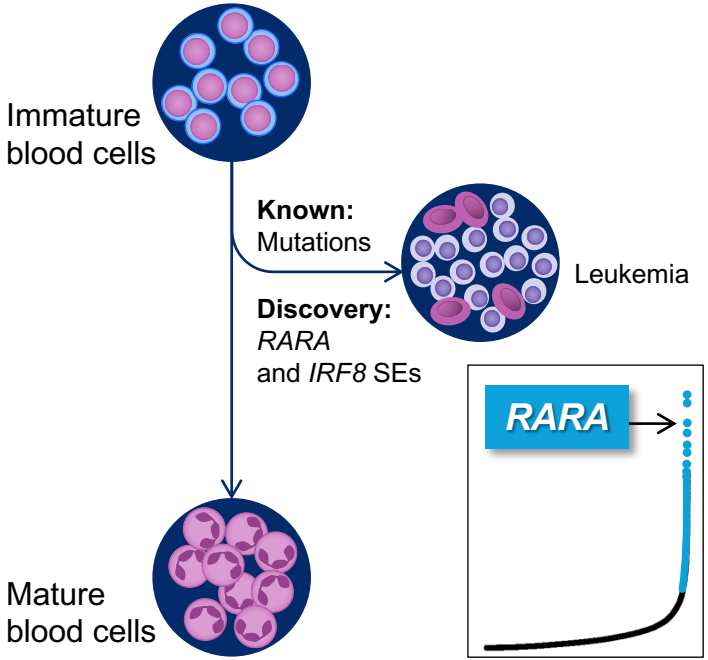
SY-1425 is approved in Japan as Amnolake® (tamibarotene) for patients with relapsed/refractory APL
* Expected to begin in Q3 2019

Realizing our vision for SY-1425 broadly in *RARA* and *IRF8* biomarker-positive AML and higher-risk MDS patients



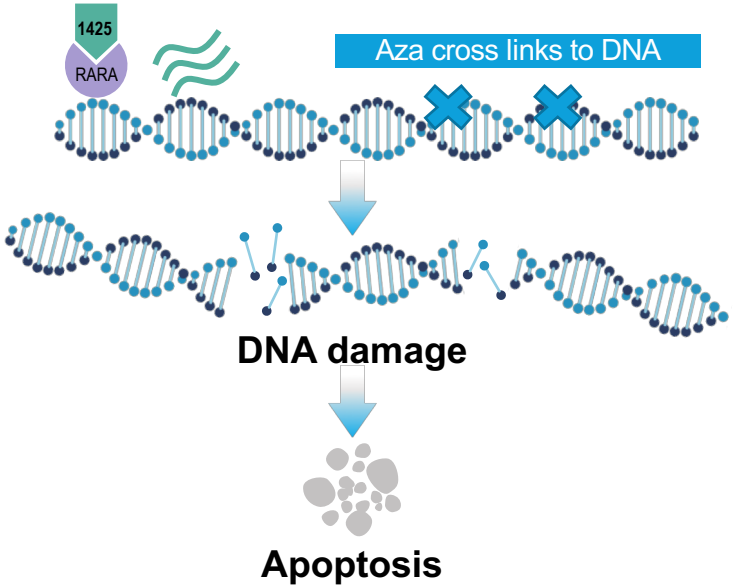
Novel combination approach leveraging *RARA* pathway activation in genomically defined subsets of AML patients

Gene control platform identifies novel patient subsets



SY-1425 enhances apoptosis preclinically

SY-1425 binds to RARα and activates differentiation genes



SY-1425 shows synergy with a range of AML therapies, including chemotherapy and targeted agents

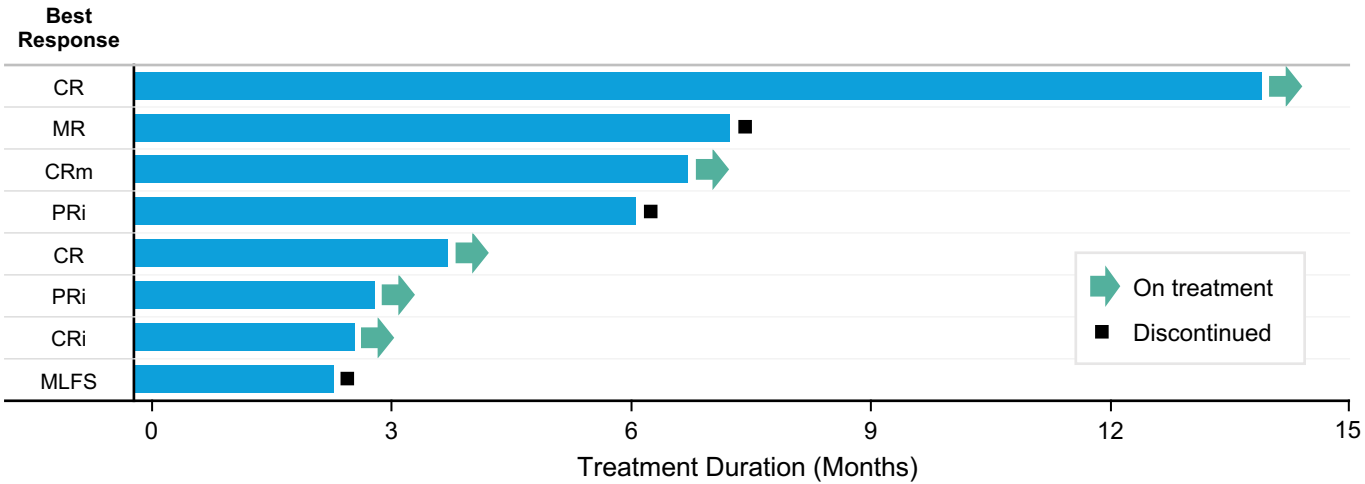
SYROS

Data published in October 2017 in Cancer Discovery

Data published in October 2018 in Haematologica

Initial data shows SY-1425 in combination with azacitidine has high response rates and rapid onset of action in biomarker-positive AML patients

Responses seen in biomarker-positive newly diagnosed, unfit AML patients



ORR (n=8)

63%

CR/CRi Rate (n=8)

50%

Time to response

1 month

- Elderly, high-risk population with median age of 76 and more than half having poor-risk cytogenetics
- Generally well-tolerated with no increased neutropenia
- Initial data compare favorably to single-agent azacitidine, which shows a response rate of 18-29%[1] in unfit AML patients with initial response generally occurring after four cycles[2]
- Initial data support *RARA* and *IRF8* biomarkers for patient selection, with 17% ORR in biomarker-negative cohort (n=6)

Data as of Oct. 29, 2018 snapshot presented in December 2018 at ASH Annual Meeting

[1] Fenaux et al, *JCO* 2010; Dombret et al, *Blood* 2015; Vidaza® (azacitidine) Prescribing Information, Celgene Revision 09/2018.

[2] Thepot et al, *AJH* 2014.

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

Fast-growing AML market is projected to be ~ $1 billion this year

Unmet need across populations

~30,000

AML patients*

R/R AML

- Clinical trials are preferred treatment strategy
- Recently approved therapies target only limited subsets of patients, with CR/CRh rates in 20-35% range and duration of 4-8 mos
- Survival remains low at < 6 mos

Targeted patient population

~35%

RARA and *IRF8* biomarker-positive**

Newly diagnosed AML

- >50% of newly diagnosed patients are elderly/unfit for intensive therapy
- High unmet medical need remains in rapidly evolving landscape
- Targeted combinations are emerging as standard-of-care
  - Despite high CR rates, duration of response remains limited

SYROS

*2018 incidence in the U.S. and the EU 5 (UK, Germany, France, Spain and Italy) from Decision Resources Group. Annual sales forecast from Decision Resources Group.
Sources: NCCN guidelines AML (Feb 2018); Clinical Lymphoma, Myeloma & Leukemia, 16:625-36 (2016); Blood 120:2454-2465 (2012); Ivosidenib, enasidenib & gilteritinib USPIs.
** Based on data from 201 evaluable patients screened in our ongoing Phase 2 clinical trial of SY-1425

Ongoing Phase 2 trial evaluating SY-1425 in combination with azacitidine in biomarker-positive AML, with opportunity for rapid proof-of-concept

- Additional data in newly diagnosed unfit AML expected in second half of 2019
- Potential proof-of-concept data in relapsed or refractory AML expected in 2020

Phase 2 clinical trial design

Patient population	Combo agent	Primary purpose
Biomarker-positive R/R AML *(25 patients)*	azacitidine	Assess safety and efficacy
Biomarker-positive newly diagnosed, unfit AML *(25 patients)*	azacitidine	Assess safety and efficacy
Biomarker-negative newly diagnosed, unfit AML *(25 patients)*	azacitidine	Support development of commercial companion diagnostic

Realizing our vision for the promise of selective CDK7 inhibition in difficult-to-treat cancers

Now

SY-1365 in multiple ovarian and breast cancer patient populations

Opportunities for rapid proof-of concept in high grade serous and clear cell ovarian cancers

Next

Combination data in earlier lines of therapy

Additional solid tumors

Blood cancers

SY-5609

Vision

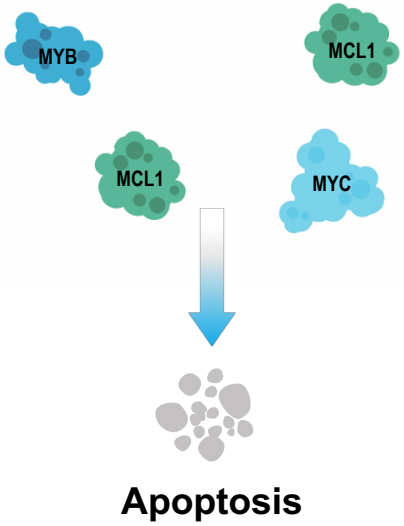
Transformative targeted approach for a range of difficult-to-treat solid tumors and blood cancers

Selective CDK7 inhibition attacks two fundamental processes in cancer

CDK7

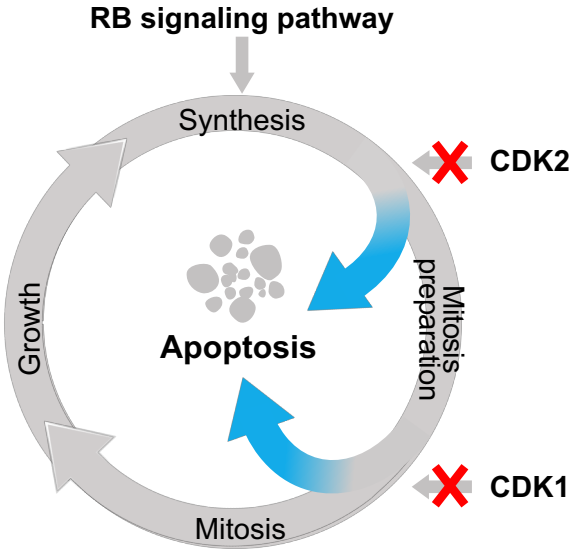
Transcription

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



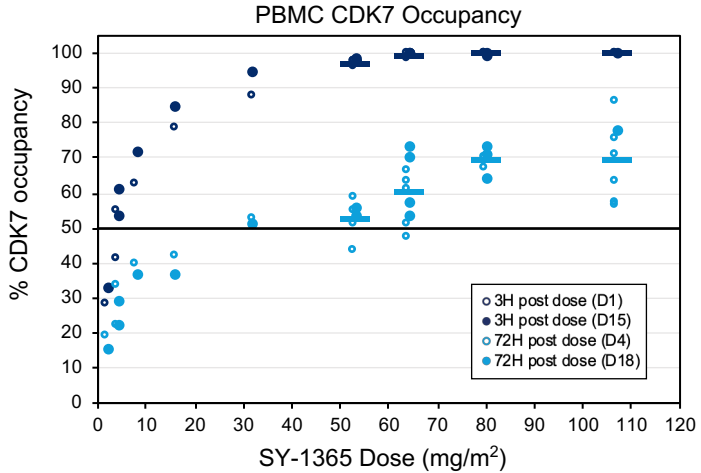
Cell cycle

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

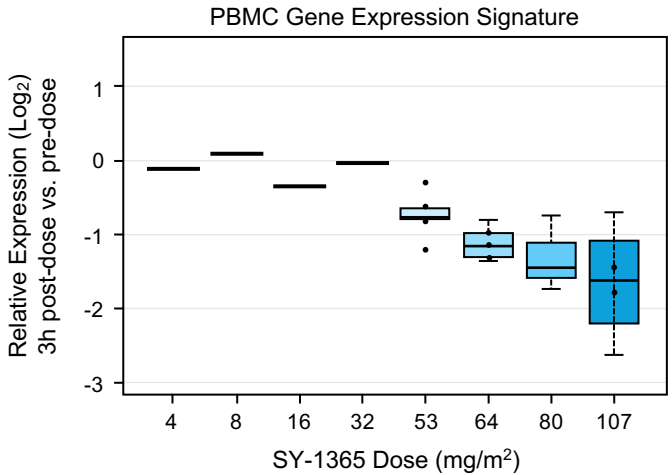


SY-1365 demonstrated proof-of-mechanism at tolerable doses in dose escalation portion of ongoing Phase 1 trial

Exceeded desired target occupancy levels at doses ≥ 32 mg/m²



Demonstrated dose-dependent downstream changes in gene expression



Adverse events (AEs) were predominantly low grade, reversible and generally manageable

- Most frequent related AEs include headache, nausea, vomiting and fatigue
- No reports of neutropenia

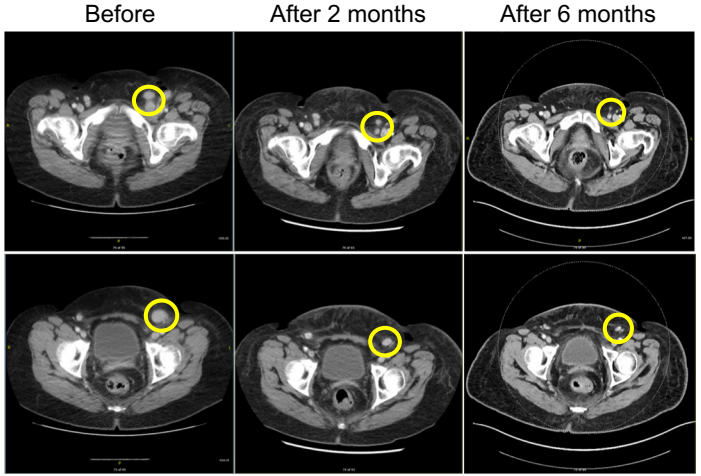
Data as of October 15, 2018; Presented in November 2018 at EORTC-NCI-AACR Symposium

SY-1365 demonstrated early evidence of clinical activity, including durable partial response in relapsed ovarian clear cell cancer patient

SY-1365 demonstrated 37% disease control rate (CR+PR+SD)

- Clinical activity per RECIST 1.1 criteria observed in 7 of 19 evaluable patients
  - 1 confirmed PR (clear cell ovarian cancer patient) observed at 80 mg/m^2 BIW
  - 6 stable disease (2 ovarian, 2 breast and 2 endometrial cancer patients), mostly at doses ≥ 32 mg/m^2 BIW
- Duration of treatment ranged from 50 - 127 days

CT images of heavily pretreated stage IV clear cell ovarian cancer patient



- Confirmed PR after 2 cycles (31.8% reduction at C3D1)
- Remained on study in PR in 7th month of SY-1365 treatment as of data snapshot (49% decrease at C7D1)
- Best response to prior therapies was stable disease

Data as of October 15, 2018; Presented in November 2018 at EORTC-NCI-AACR Symposium

Significant need for new therapies in ovarian cancer and HR-positive metastatic breast cancer

Ovarian and HR-positive breast cancers represent > $8 billion fast-growing market

Ovarian cancer

>60,000
patients

High-grade serous

- Most patients present with advanced disease at initial diagnosis
- Platinum-based therapy is foundation of care
  - Majority of patients, even those who initially respond, eventually relapse
- Continued unmet need for improved initial treatment for patients with relapsed disease and for non-BRCA mutated patients

Clear cell

- ~10% of ovarian cancer in North America
- Relatively chemo-resistant with poor prognosis
- Fewer than 10% of patients with relapsed disease respond and PFS is ~2-4 months
- Little in the clinical pipeline for these patients

HR+ metastatic breast cancer

~58,000
patients

- Standard of care includes CDK4/6 inhibitor plus an aromatase inhibitor
  - Half of patients relapse with ~2 years
- Second-line hormone-based therapies have limited efficacy
  - Emerging therapies limited to targeted patient subsets

2018 incidence in the U.S., Japan and the EU 5 (UK, Germany, France, Spain and Italy) from Decision Resources Group. Annual sales forecast from Decision Resources Group.

Sources: NCCN Guidelines Ovarian Cancer (Mar 2018). Gabra H. EJC Suppl. 2014 Dec;12(2):2-6. and Herzog TJ and Monk BJ. Onitilo AA et al., Clin Med Res 2009; 7(1-2):4-13. Rugo HS et al., JCO 2016; 34: 3069-3103. Finn RS et al, N Engl J Med 2016; 375(20): 1925-1936. Faslodex USPI. Takano et al., Int J Gynecol Cancer 2008;18:937–942. Konstantinopoulos et al., Gynecologic Oncology150 (2018) 9–13. Tan et al., J Clin Oncol. 2014;32(15 Suppl). Okamoto et al., Int J Gynecol Cancer 2014;24: S20-S25. Sugiyama et al. Cancer2000; 88:2584–9.

SYROS

Phase 1 trial explores SY-1365 in multiple ovarian and breast cancer patient populations, providing two potential rapid proof-of-concept opportunities

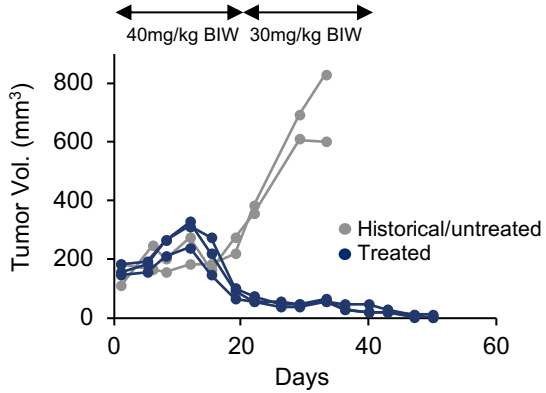
- Initial data from relapsed HGSOC and biopsy cohorts expected in Q4 2019, with additional data expected in 2020
- Potential proof-of-concept data in clear cell and relapsed HGSOC (3+ prior lines) expected in 2020
- Initial data from HR-positive breast cancer cohort expected in 2020

Ongoing expansion cohorts

Patient population	Single/combo agent	Target enrollment
Relapsed ovarian clear cell cancer	Single agent	N=12
Relapsed HGSOC, 3+ prior lines	Single agent	N=24
Relapsed HGSOC, 1+ prior lines (platinum sensitive)	Combination with carboplatin	N=24
HR+ metastatic breast cancer, CDK4/6 inhibitor resistant	Combination with fulvestrant	N=12
Solid tumors accessible for biopsy	Single agent	N=30

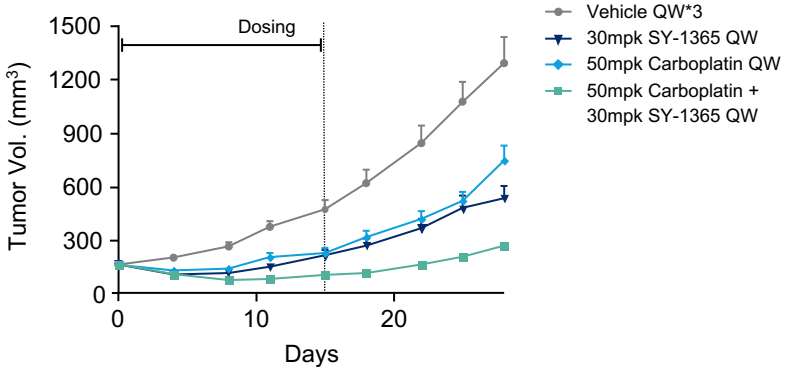
SY-1365 shows anti-tumor activity as single agent and in combination with standard-of-care in ovarian models, supporting ongoing clinical investigation

SY-1365 induces tumor growth inhibition, including complete regressions, in heavily pretreated ovarian cancer models



- Sensitivity to SY-1365 was associated with RB pathway alterations
  - Approximately 2/3 of high-grade serous ovarian cancer patients have RB alterations[1]
- Responses observed in 10/17 (59%) models, irrespective of BRCA status or PARP inhibitor sensitivity

Weekly SY-1365 in combination with carboplatin enhances activity in ovarian cancer xenograft models



- SY-1365 inhibited DNA repair and transcription of HRR genes in preclinical models, inducing an HRD-like state that may increase sensitivity to DNA-damaging agents and DNA repair inhibitors

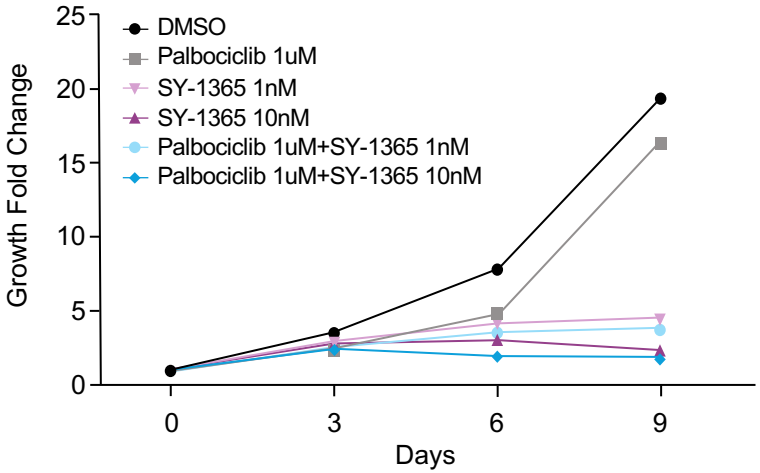
Data presented in April 2018 at the American Association of Cancer Research (AACR) Annual Meeting

[1]TCGA Ovarian Cancer Integrated Analysis, Nature 2011

Data presented in November 2018 at EORTC-NCI-AACR Symposium

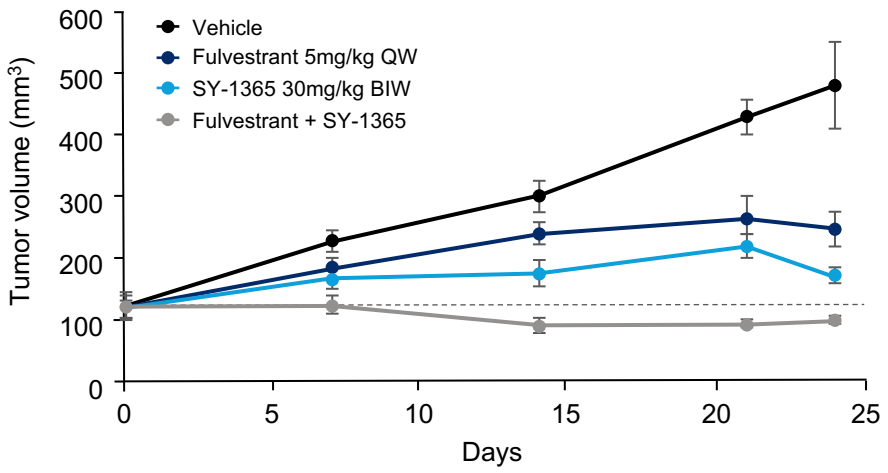
SY-1365 shows anti-tumor activity and synergy with fulvestrant in HR-positive breast cancer models, including CDK4/6 inhibitor resistant models

SY-1365 inhibits growth of CDK4/6 inhibitor resistant breast cancer cell models



Approximately 1/3 of HR+ breast cancer patients have RB/cell cycle alterations post CDK4/6 inhibitors

HR-positive cell-derived xenograft model



In vitro synergy was seen in several HR+ breast cancer cell lines

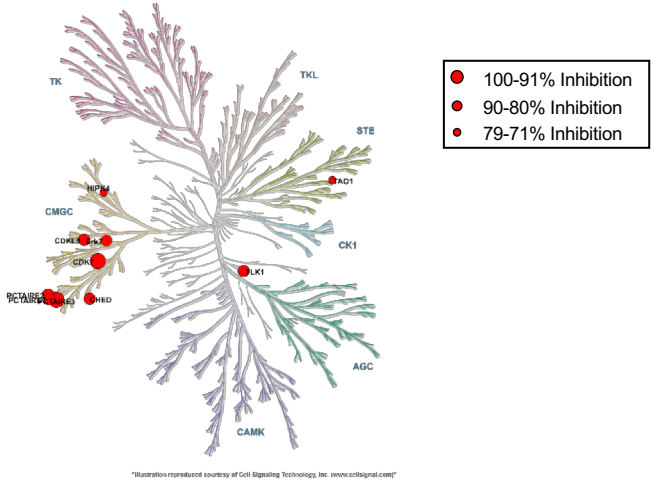
Data presented by Syros' collaborators at Dana-Farber Cancer Institute in December 2018 at San Antonio Breast Cancer Symposium

Source: Jeselsohn et al, 2018; Data from collaboration with Dana-Farber Cancer Institute

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

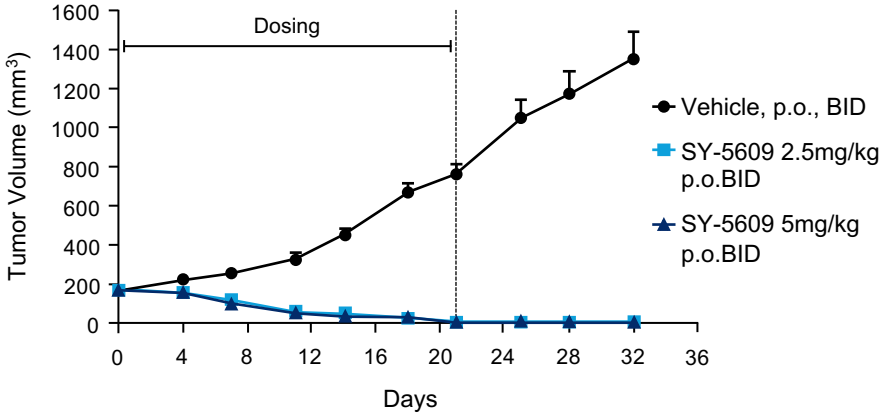
- Significant opportunity for adding an oral approach across a range of solid tumors and blood cancers
- Expect to initiate a Phase 1 oncology trial for SY-5609 in early 2020

SY-5609 is a potent and highly selective oral CDK7 inhibitor



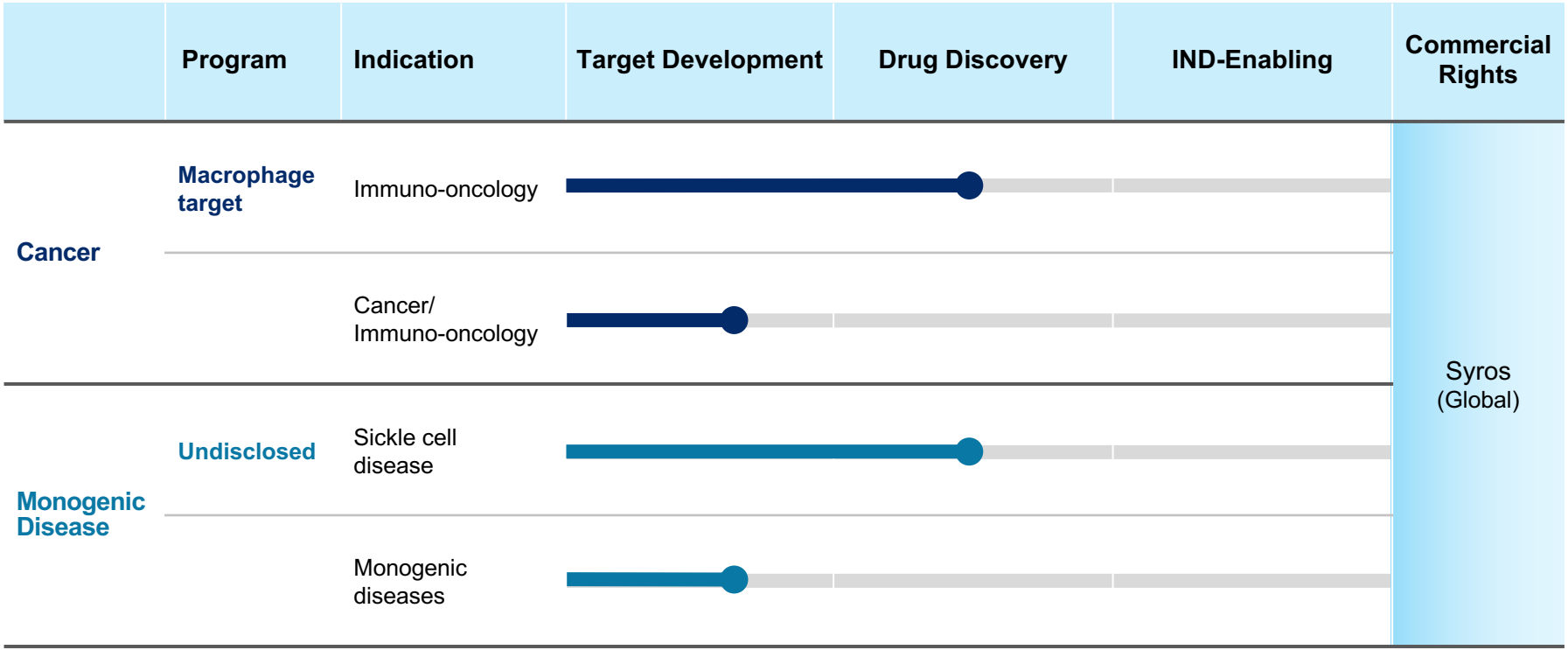
- Only 4 of 485 kinases inhibited at > 90%
- > 4,000-fold more selective for CDK7 over other CDKs

SY-5609 demonstrates anti-tumor activity, including complete regressions, in a breast cancer model



Data presented in November 2018 at EORTC-NCI-AACR Symposium

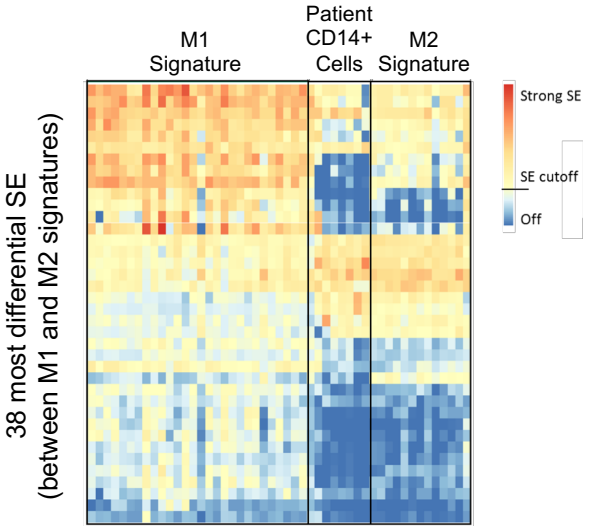
Robust early-stage pipeline to fuel long-term growth



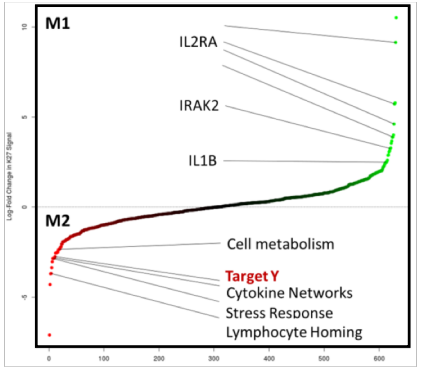
Immuno-oncology strategy: Modulate tumor and immune cells to pro-inflammatory state to promote tumor killing

- 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



Small molecule inhibitor switches immunosuppressive macrophages to pro-inflammatory state



- Syros-developed inhibitors of Target Y have shown tumor growth inhibition in *in vivo* preclinical models

Data presented in October 2017 at the American College of Surgeons (ACS) Clinical Congress

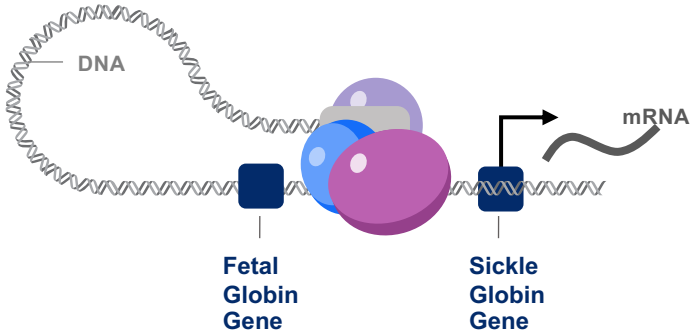
SYROS

Monogenic disease strategy: Alter expression of a single gene for therapeutic benefit

Sickle cell disease (SCD)

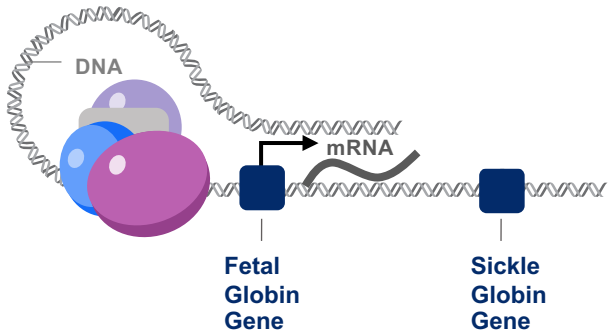
Clinical and genetic data point to therapeutic benefit of elevated fetal globin

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

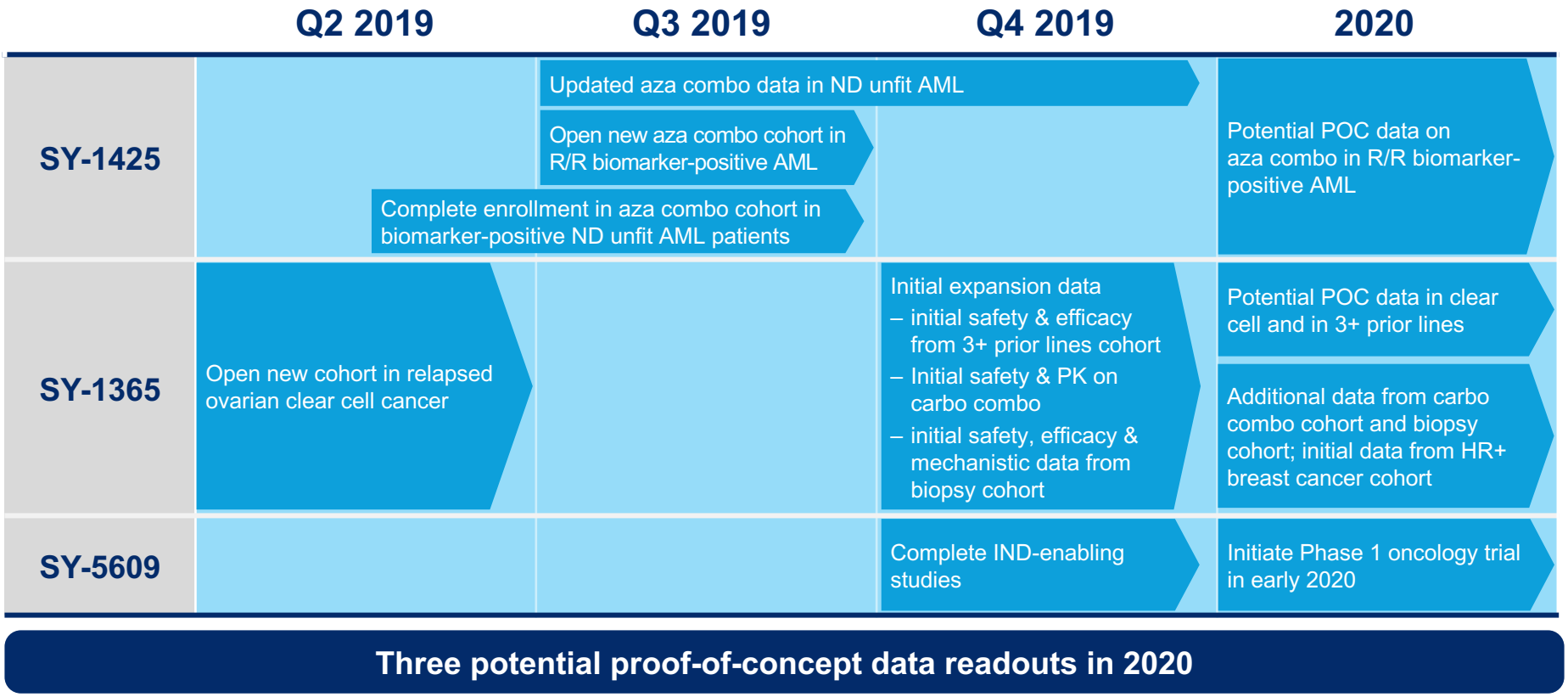


Using transcriptional chemistry platform to control globin expression

- Characterized transcriptional programs that determine globin expression in fetal and adult states
- Identifying gene regulatory interactions at the globin locus
- Targeting transcriptional regulators with small molecules at the globin genes



Multiple clinical milestones expected in 2019 and 2020



Three potential proof-of-concept data readouts in 2020

Rapidly advancing toward our vision

Vision

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

Next

- Progressing to pivotal development
- Advancing multiple programs in clinic
- Preparing for commercial launch
- Continued investment in discovery

Now

- Driving SY-1425 and SY-1365 to key milestones
- Advancing SY-5609 toward clinical development
- Investing in discovery to support goal of one IND every other year
- Capital to fund planned operations into Q2 2020

SYROS


SYROS