An Expression Makes a World of Difference

May 2020

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-1425 and SY-5609, under the timelines we project in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of our drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; obtain and maintain patent protection for our drug candidates and the freedom to operate under third party intellectual property; obtain and maintain necessary regulatory approvals; identify, enter into and maintain collaboration agreements with third parties, including our ability to perform under our collaboration agreements with Incyte Corporation and Global Blood Therapeutics; manage competition; manage expenses; raise the substantial additional capital needed to achieve our business objectives; attract and retain qualified personnel; and successfully execute on our business strategies; risks described under the caption “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2019 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2020, each of which is on file with the Securities and Exchange Commission (SEC); and risks described in other filings that we may make with the SEC in the future.

In addition, the extent to which the COVID-19 outbreak continues to impact our workforce and our discovery research, supply chain and clinical trial operations activities, and the operations of the third parties on which we rely, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the outbreak, additional or modified government actions, and the actions that may be required to contain the virus or treat its impact.

Any forward-looking statements contained in this presentation speak only as of the date this presentation is made, and we expressly disclaim any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

Our Vision

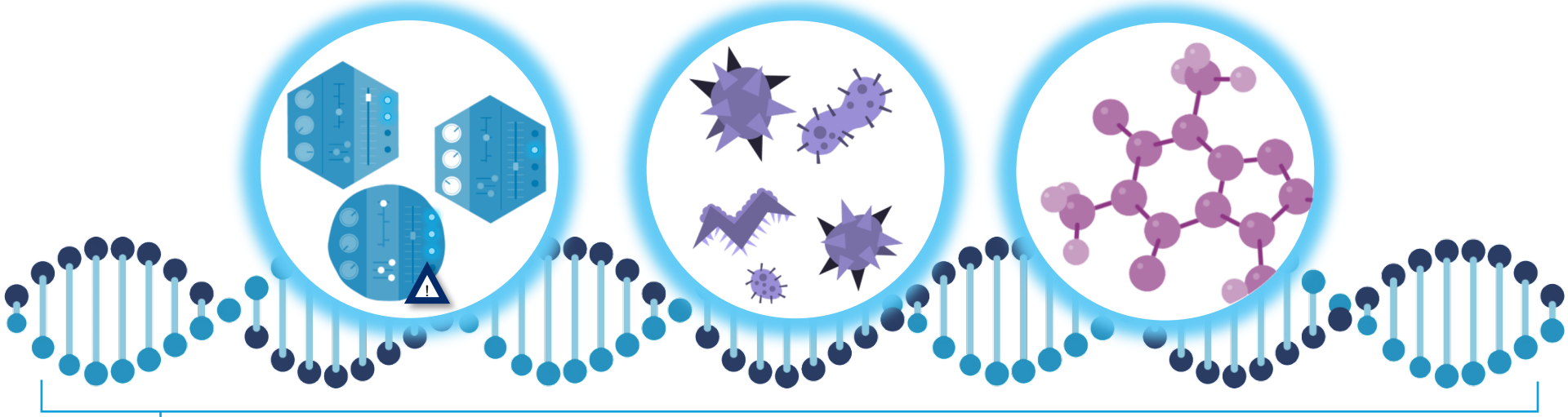
To create unparalleled value for patients, employees and shareholders by creating transformative medicines for severe disease through our world-leading expertise in gene control and our exceptional people and culture

Redefining the power of small molecules to control expression of genes

Regulatory Genomics

Disease Biology

Transcriptional Chemistry



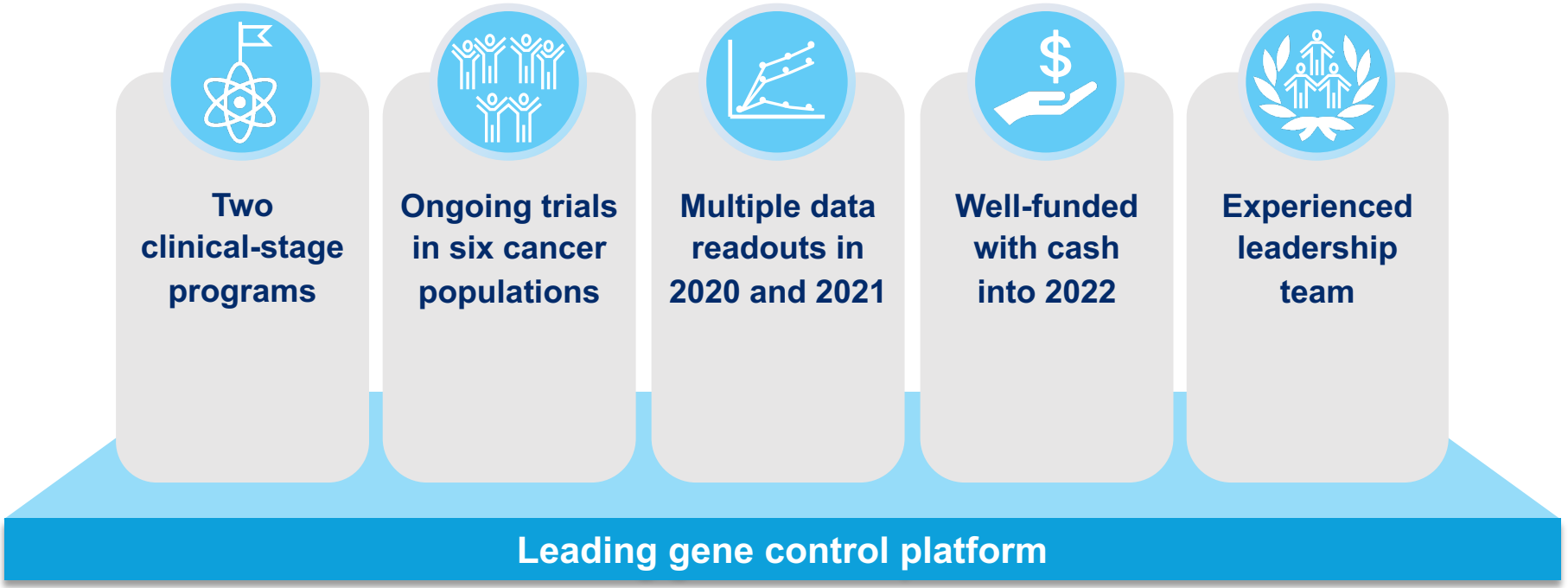
98% Previously unexplored regulatory regions of the genome control expression of genes determining cell function; majority of disease variation found in these regions

Patient Impact

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

SYROS

Syros today: Clear vision, growing pipeline, pioneering platform

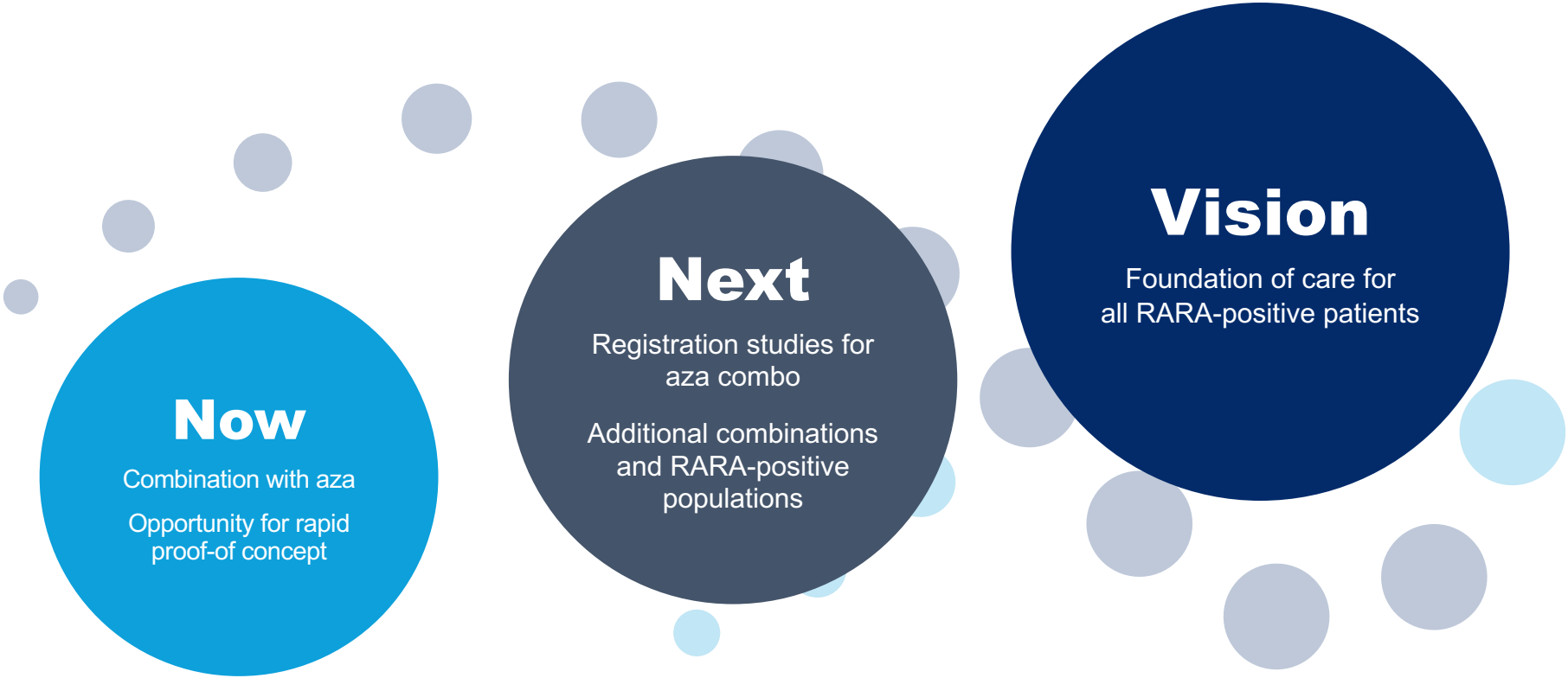


Deep gene control pipeline

Program	Indication	Drug Discovery	IND-Enabling	Early Clinical	Mid-Clinical	Pivotal	Commercial Rights
SY-1425 (RARα agonist)	Newly diagnosed unfit AML						SYROS N. America & Europe
	R/R AML						
SY-5609 (Oral CDK7 inhibitor)	Select solid tumors						SYROS
CDK12/13 inhibitor	Cancer						SYROS
Macrophage target	Cancer/immune modulation						SYROS
LRF & NuRD modulators	Sickle cell disease & beta thalassemia						GBT Syros US co-promote option
Triplet repeat modulator	Myotonic dystrophy type 1						SYROS

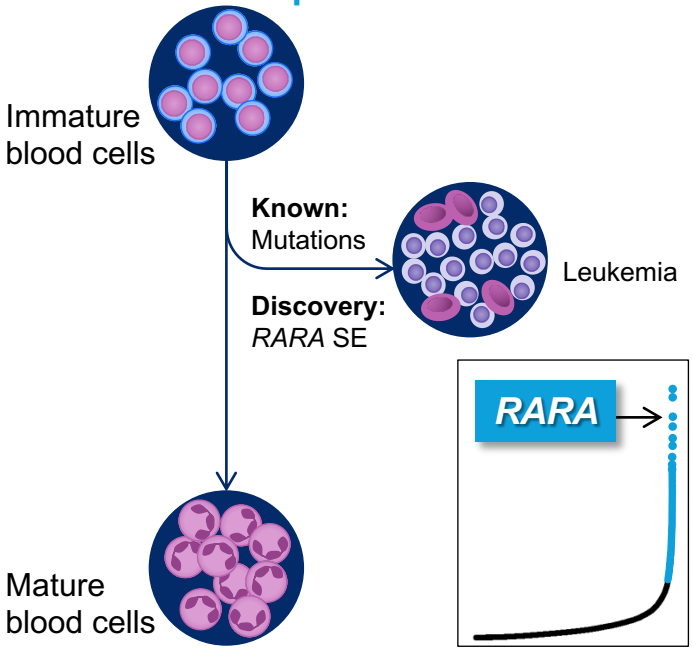
SY-1425 is approved in Japan as Amnolake® (tamibarotene) for patients with relapsed/refractory APL

Our vision for SY-1425 in RARA-positive patients

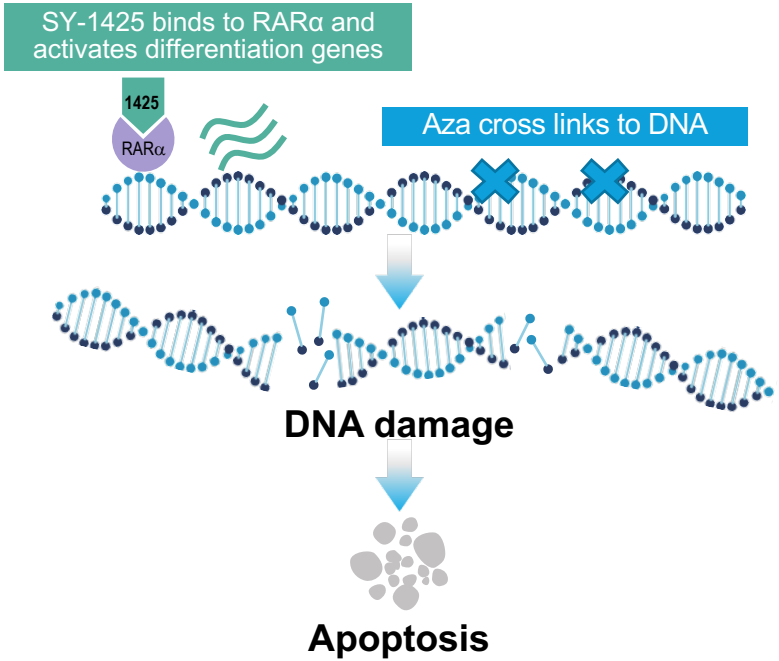


Novel combination approach for RARA-positive AML patients

Gene control platform identifies novel patient subset



SY-1425 enhances apoptosis preclinically

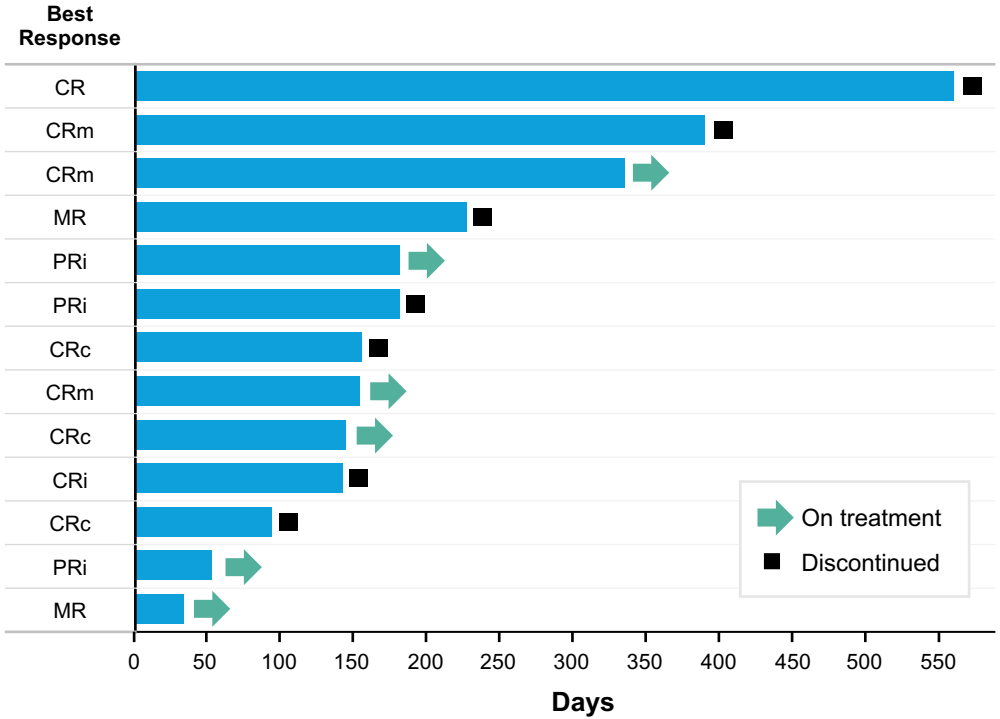


SY-1425 shows synergy with a range of AML therapies in preclinical studies

Data published in October 2017 in Cancer Discovery

Data published in October 2018 in Haematologica

SY-1425 in combination with azacitidine shows high complete response rates, deep CRs and rapid onset of action in RARA-positive AML patients



62%
CR/CRi Rate (n=13)

54%
CR Rate (n=13)

82%
Transfusion independence (n=11)

1 month
Time to response

86% of CRs were deep molecular or cytogenetic CRs
Duration of response up to 344 days, with three CRs lasting more than seven months as of data cut-off

Data published in October 2019 at ESH

Combination has been generally well-tolerated with no evidence of increased toxicities

Preferred Term	All Grades N = 40 n (%)	≥ Grade 3 N = 40 n (%)
Patients with an AE	40 (100)	29 (73)
Hematologic		
Thrombocytopenia	11 (28)	10 (25)
Anemia	9 (23)	9 (23)
Febrile neutropenia	9 (23)	9 (23)

AEs consistent with single-agent SY-1425 or azacitidine in AML

Rates of myelosuppression comparable to reports of single-agent azacitidine

Majority of non-hematologic AEs were low grade

Preferred Term	All Grades N = 40 n (%)	≥ Grade 3 N = 40 n (%)
Patients with an AE	40 (100)	29 (73)
Non-Hematologic		
Nausea	15 (38)	0 (0)
Decreased appetite	15 (38)	3 (8)
Constipation	13 (33)	0 (0)
Fatigue	13 (33)	5 (13)
Edema peripheral	12 (30)	0 (0)
Diarrhea	11 (28)	1 (3)
Pyrexia	11 (28)	2 (5)
Hypertriglyceridemia	11 (28)	6 (15)
Dizziness	10 (25)	0 (0)
Arthralgia	9 (23)	1 (3)
Dyspnea	9 (23)	2 (5)
Dry skin	9 (23)	0 (0)
Rash	9 (23)	1 (3)
Pruritus	8 (20)	0 (0)

Data published in October 2019 at ESH

Deep CRs and high CR rates in RARA-positive patients support RARA as the optimal biomarker for patient selection

Best IWG Response	RARA Positive n (%)	RARA Negative n (%)
Response Evaluable	13	22
ORR	8 (62)	8 (36)
CR/CRi	8 (62)	6 (27)
CR	7 (54)	3 (14)
CRm	3 (23)	0 (0)
CRc	3 (23)	3 (14)
CRi	1 (8)	3 (14)

- 27% CR/CRi rate in RARA-negative consistent with single-agent azacitidine[1]
- RARA is not a prognostic biomarker in AML, based on analyses of TCGA, BeatAML and company data
- RARA does not appear to enrich for genes that may be associated with responsiveness to azacitidine

SYROS

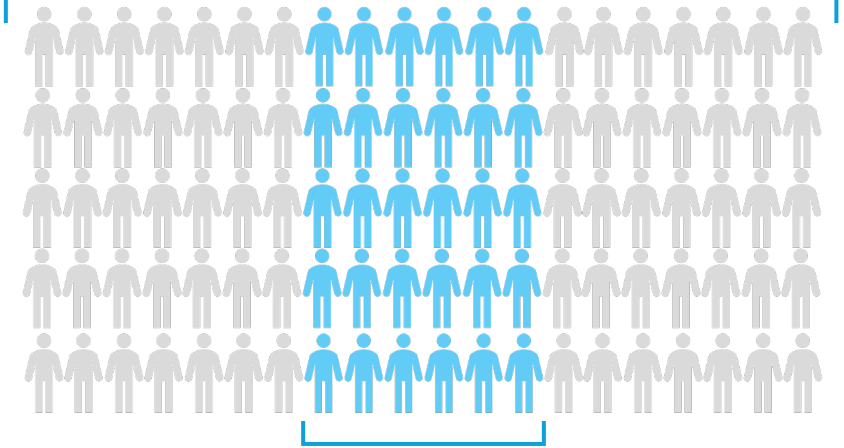
Data published in October 2019 at ESH

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

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

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

~30,000 AML patients in US and EU5



~30%
RARA-positive

R/R AML

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

Newly diagnosed AML

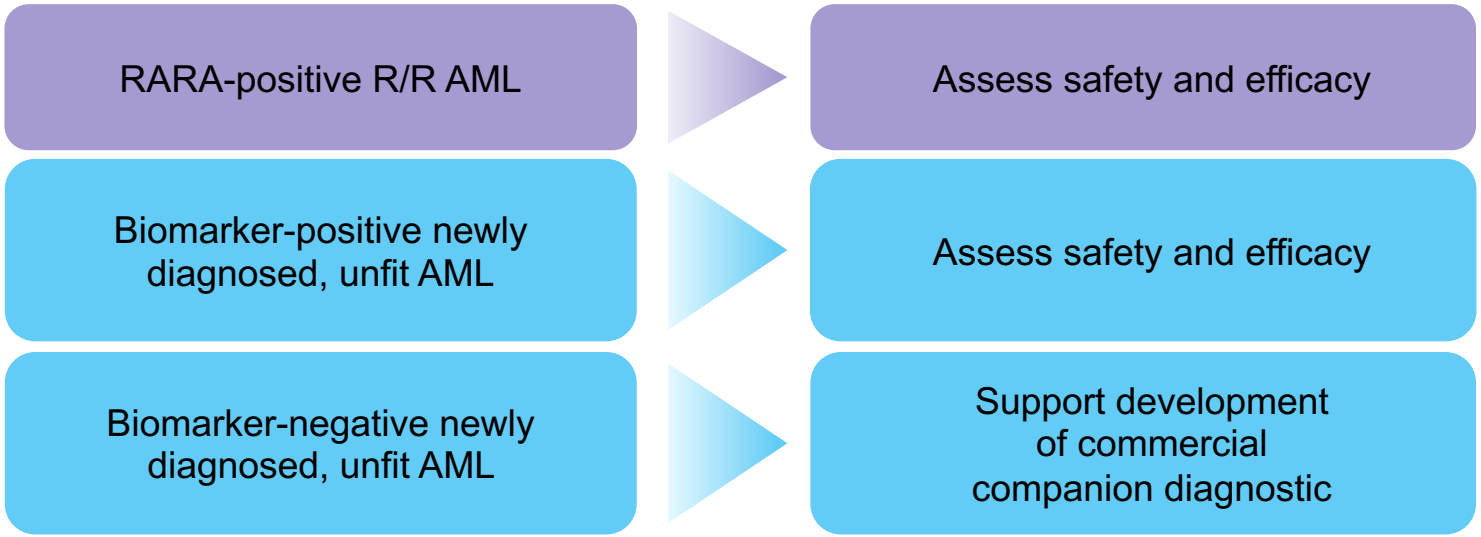
- >50% newly diagnosed patients are elderly/unfit
- Combinations emerging as standard-of-care
  - Despite high CR rates, duration of response limited

Sources: Annual sales forecast and 2018 incidence in the U.S. and the EU 5 (UK, Germany, France, Spain and Italy) from Decision Resources Group; Prevalence of RARA-positive AML patients based on data from 350 patients screened as of September 2019 in our ongoing Phase 2 clinical trial of SY-1425; NCCN guidelines AML (Feb 2018); Clinical Lymphoma, Myeloma & Leukemia, 16:625-36 (2016); Blood 120:2454-2465 (2012); Ivosidenib, enasidenib & gilteritinib USPIs.

Ongoing Phase 2 trial with opportunity for rapid proof-of-concept

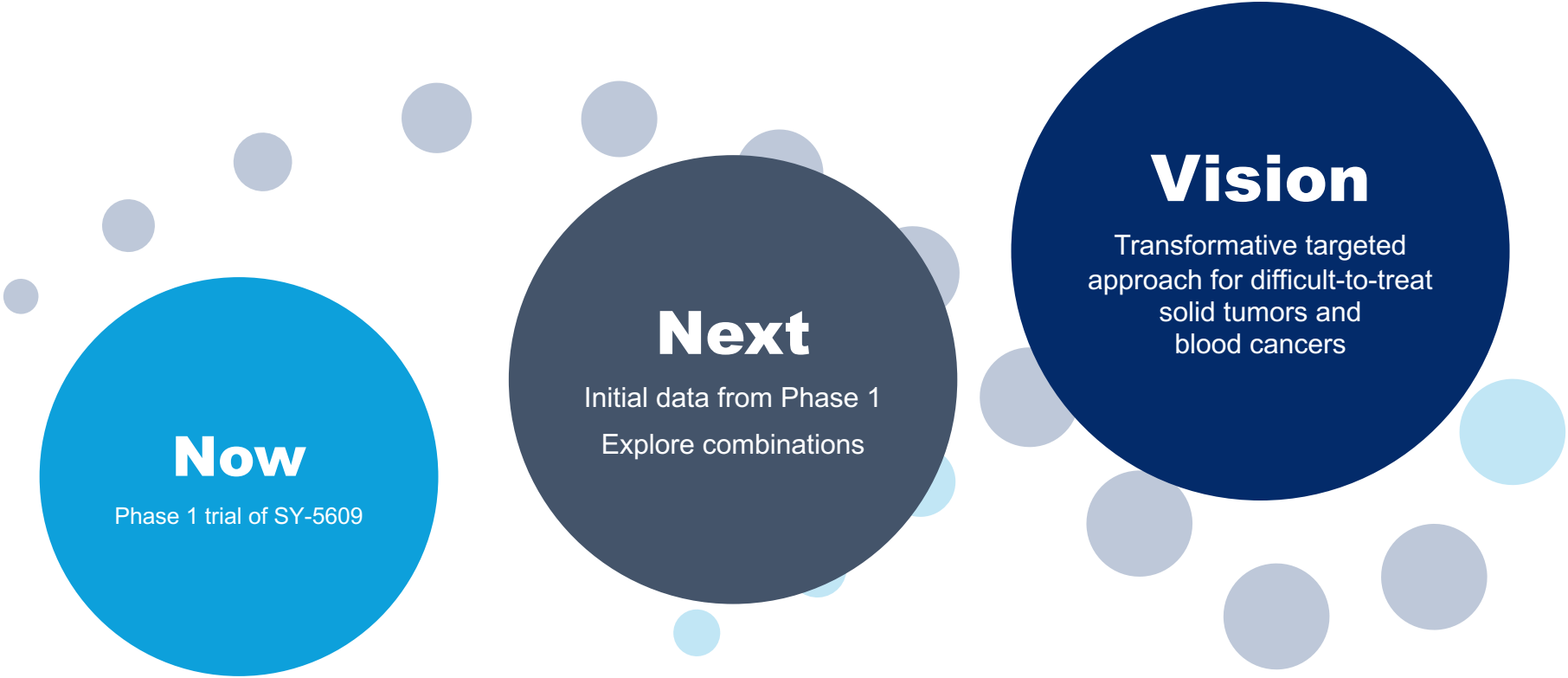
- Enrollment complete in R/R AML cohort; potential proof-of-concept data expected in Q4 2020
- Enrollment complete in newly diagnosed unfit cohorts; mature data expected in Q4 2020

Phase 2 clinical trial design



(25-patient cohorts)

Our vision for selective CDK7 inhibition in difficult-to-treat cancers



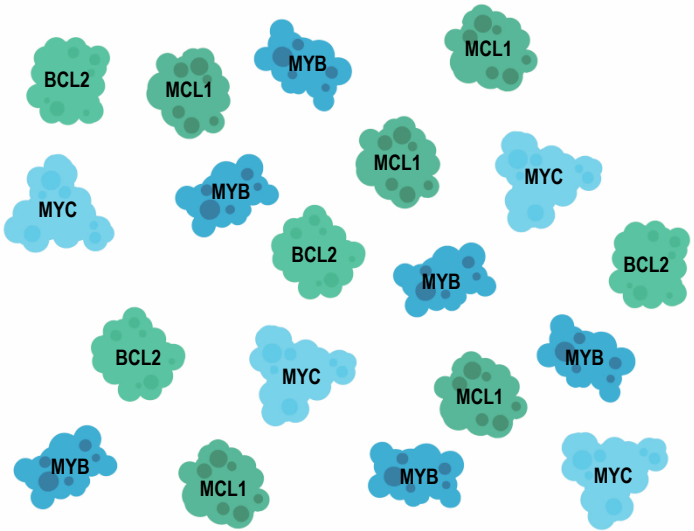
Selective CDK7 inhibition attacks two fundamental processes in cancer

Transcription

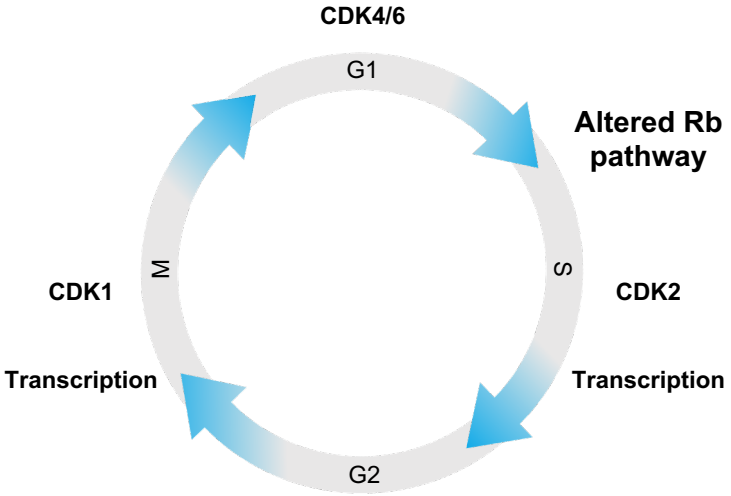
CDK7

Cell Cycle

Cancer can hijack transcriptional machinery to drive increased expression of oncogenic transcription factors and anti-apoptotic proteins



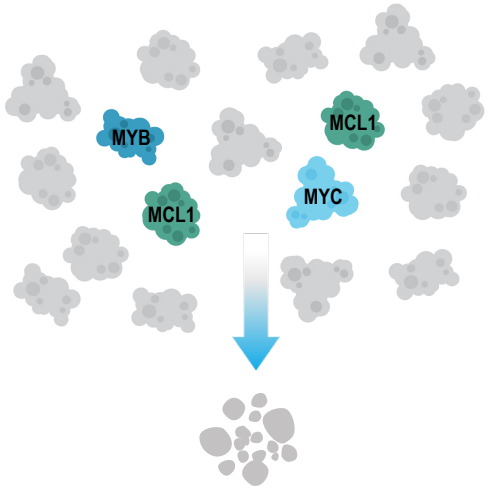
Cancer can also alter the Rb signaling pathway to progress unchecked through the cell cycle despite damaged DNA and genomes



Selective CDK7 inhibition attacks two fundamental processes in cancer

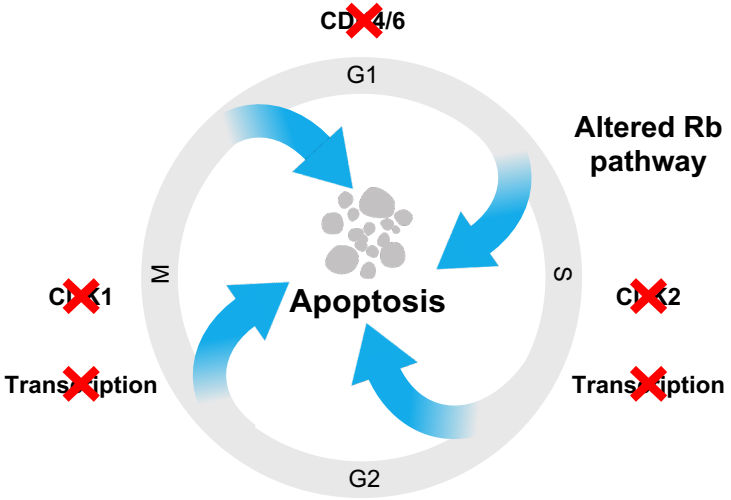
Transcription

CDK7i has been shown preclinically to decrease expression of these transcription factors and proteins

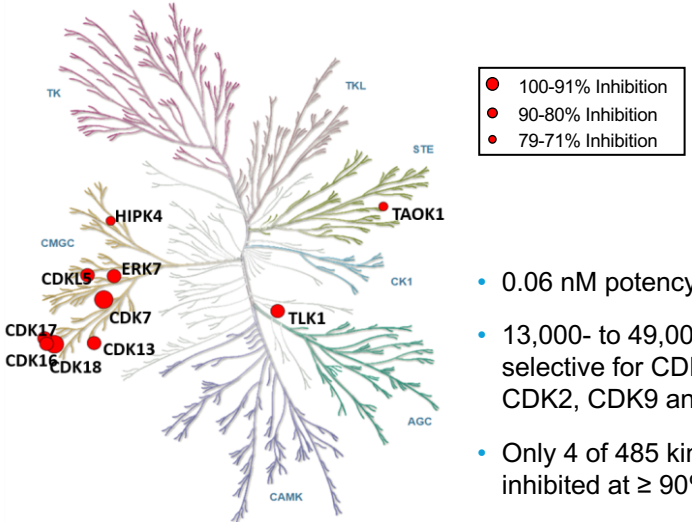


Cell Cycle

CDK7i disrupts the CDK and transcriptional activity needed to progress through the cell cycle



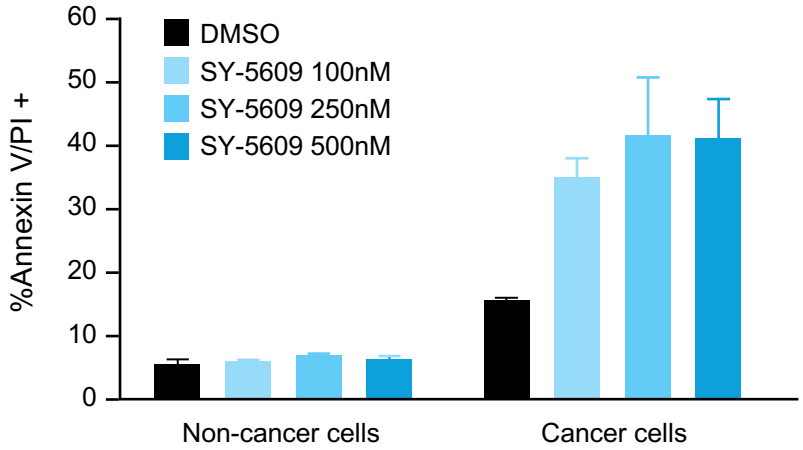
SY-5609: A highly selective oral CDK7 inhibitor with best-in-class potential



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

- 0.06 nM potency for CDK7
- 13,000- to 49,000-fold more selective for CDK7 over CDK2, CDK9 and CDK12
- Only 4 of 485 kinases inhibited at ≥ 90%

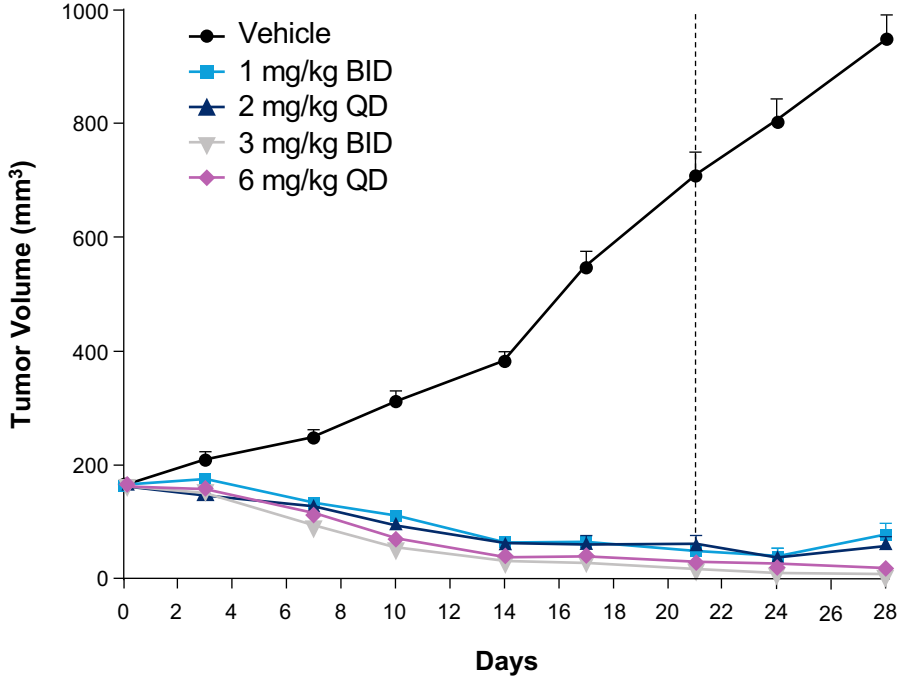
Induced apoptosis in cancer cells but not in non-cancer cells



Data presented in October 2019 at EORTC-NCI-AACR Conference

Tumor growth inhibition observed below MTD in preclinical models

Triple negative breast cancer model



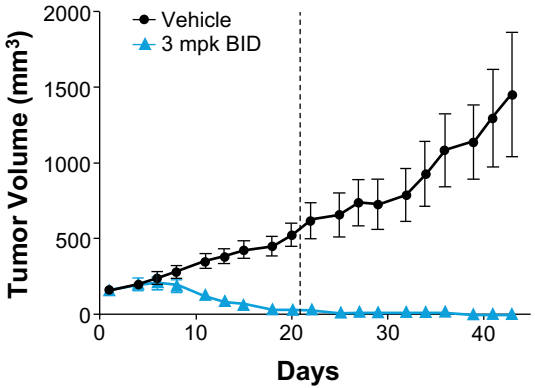
- Regressions observed at 5-fold below MTD of ≥10 mg/kg QD

Dashed lines represent end of treatment

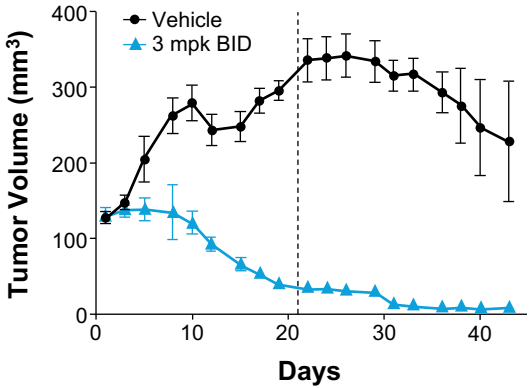
Data presented in October 2019 at EORTC-NCI-AACR Conference

Robust anti-tumor activity, including complete regressions, in preclinical models of multiple solid tumors

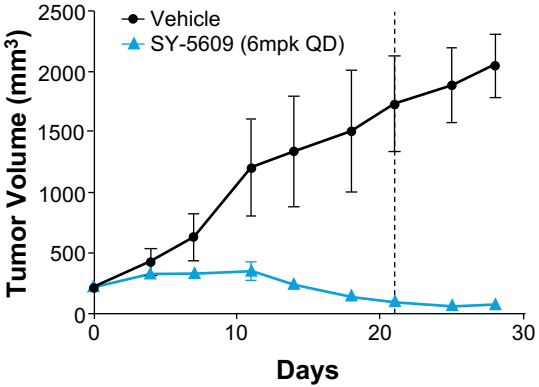
Small-cell lung cancer model



High-grade serous ovarian cancer model



Colorectal cancer model



100% (12/12) models tested demonstrated substantial tumor growth inhibition

58% (7/12) demonstrated deep and sustained regressions

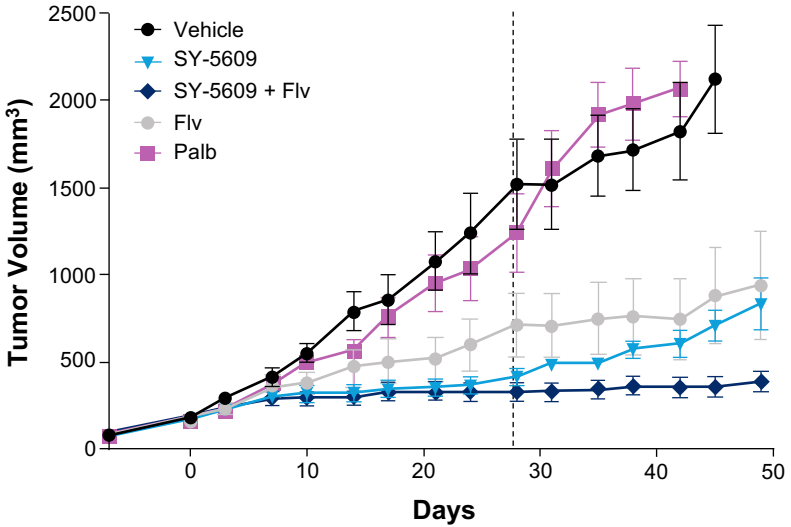
Internal company data

Data presented in October 2019 at EORTC-NCI-AACR Conference

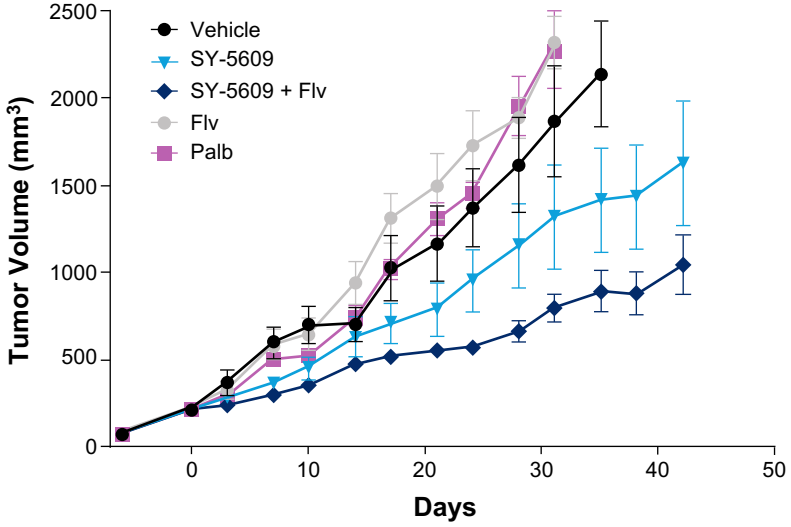
------ Dashed lines represent end of treatment

Robust responses in preclinical treatment-resistant ER+ breast cancer models

CDK4/6 inhibitor resistant model



CDK4/6 inhibitor and hormonal resistant model

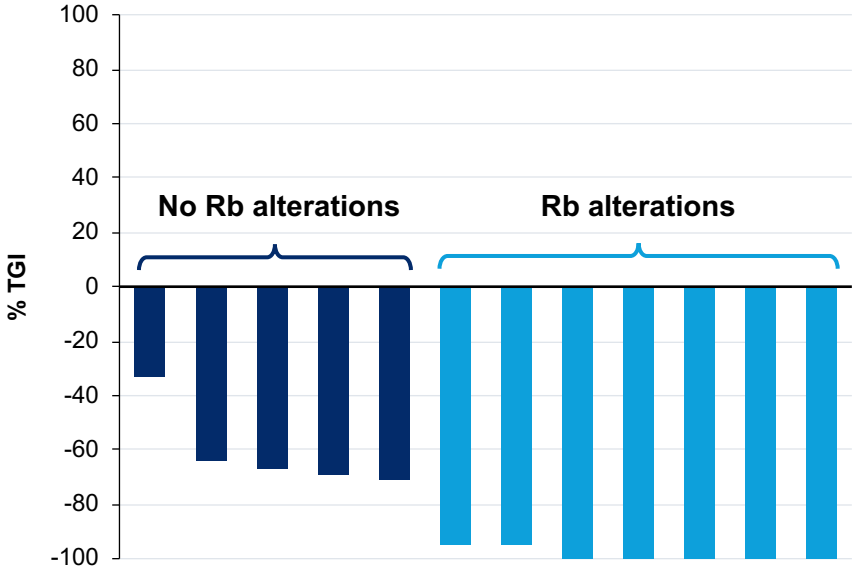


Palb: palbociclib, 50mg/kg once daily, oral; **Flv**: fulvestrant, 2.5mg/kg once weekly, sub-cutaneuous, **SY-5609**: 6 mg/kg once daily, oral

Data presented in October 2019 at EORTC-NCI-AACR Conference

Deeper and more sustained responses associated with Rb alterations in preclinical studies of breast, lung and ovarian cancers

Tumor growth inhibition in all breast, lung and ovarian cancer PDX models tested



Supports planned Phase 1 trial enriched for populations with Rb alterations

- 29% of basal breast cancer patients[1]
- ~1/3 of HR+ breast cancer patients post CDK4/6 inhibitors[2]
- 75-90% of small cell lung cancer patients[3]
- 67% of high-grade serous ovarian cancer patients[4]

[1]TCGA Breast Cancer Integrated Analysis, Nature 2012
[2] Spring et al., San Antonio Breast Cancer Symposium 2018
[3]Cancer Med. 2019 Apr; 8(4): 1459–146
[4]TCGA Ovarian Cancer Integrated Analysis, Nature 2011

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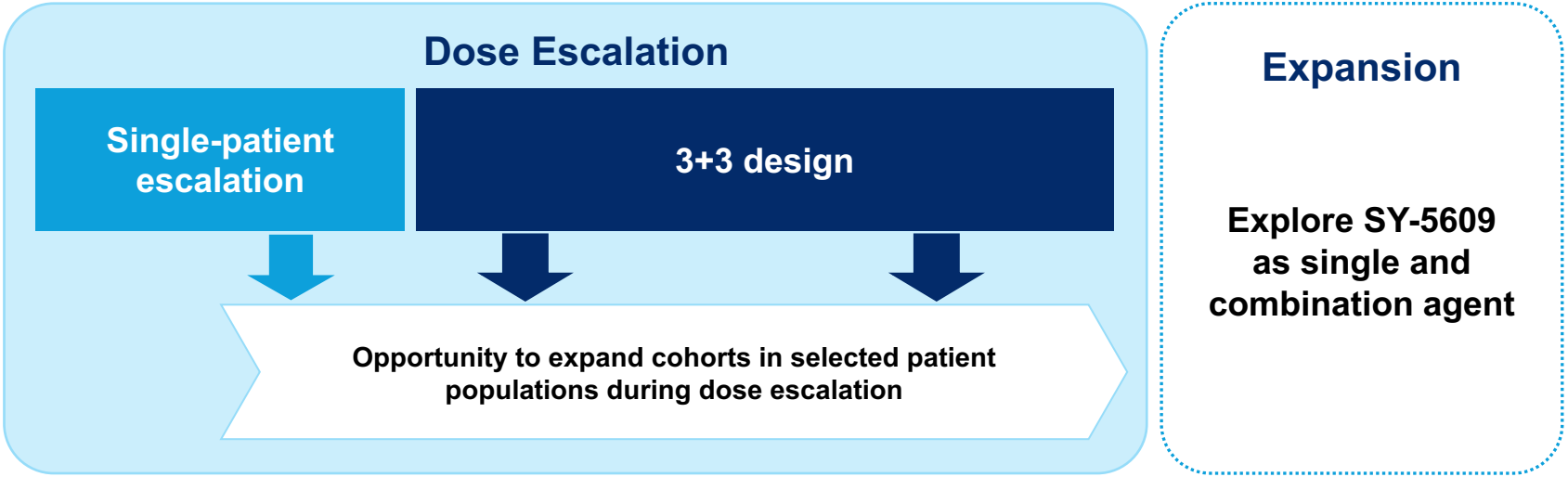
Data presented in October 2019 at EORTC-NCI-AACR Conference

Ongoing Phase 1 trial in select solid tumors



- Focused on breast, lung, colorectal and ovarian cancers and any solid tumors with Rb alterations
- PK/PD guided dose escalation
- Initial safety, tolerability and PK/PD data expected in Q4 2020
- Additional dose escalation data, including clinical activity, expected in mid-2021

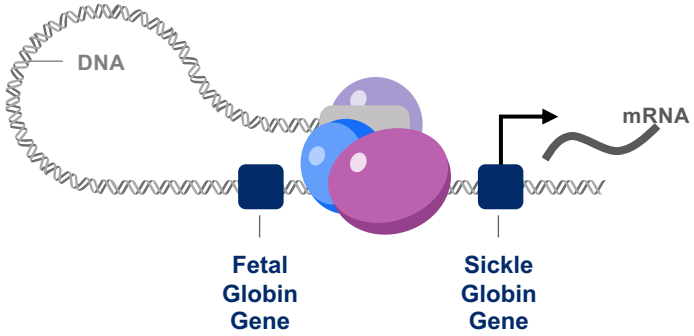
Robust early-stage pipeline to fuel long-term growth

Therapeutic Area	Program	Target Development	Drug Discovery	IND-Enabling	Commercial Rights
Cancer	CDK12/13 inhibitor				SYROS
	Target 1				SYROS
	Target 2				SYROS
	Target 3				SYROS
	Myeloproliferative neoplasms				Incyte
Cancer/Immune modulation	Macrophage target				SYROS
Monogenic Disease	Sickle cell disease & beta thalassemia				GBT Syros US co-promote option
	Myotonic dystrophy type 1				SYROS

Discovering an oral medicine to turn on fetal globin gene with aim of providing a functional cure for sickle cell disease and beta thalassemia

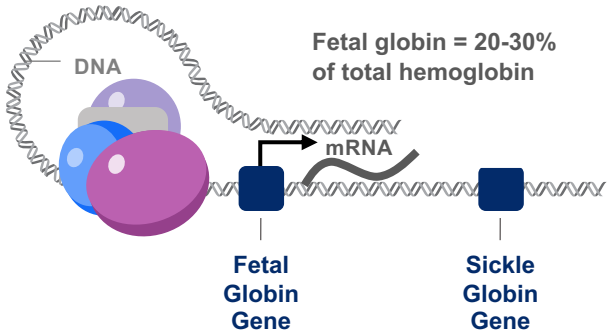
Clinical and genetic data point to therapeutic benefit of elevated fetal globin

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



Using gene control platform to elevate fetal globin expression

- Characterized transcriptional programs that determine globin expression in fetal and adult states
- Identified and targeting LRF and components of the NuRD complex with small molecules



Expanding our efforts in sickle cell disease and beta thalassemia through collaboration with Global Blood Therapeutics

- $20 million upfront
- Up to $40 million in preclinical research funding over at least three years
- Up to $315 million in option exercise fee and milestone payments per product
- Mid- to high-single digit royalties on sales
- Option to co-promote first product in US

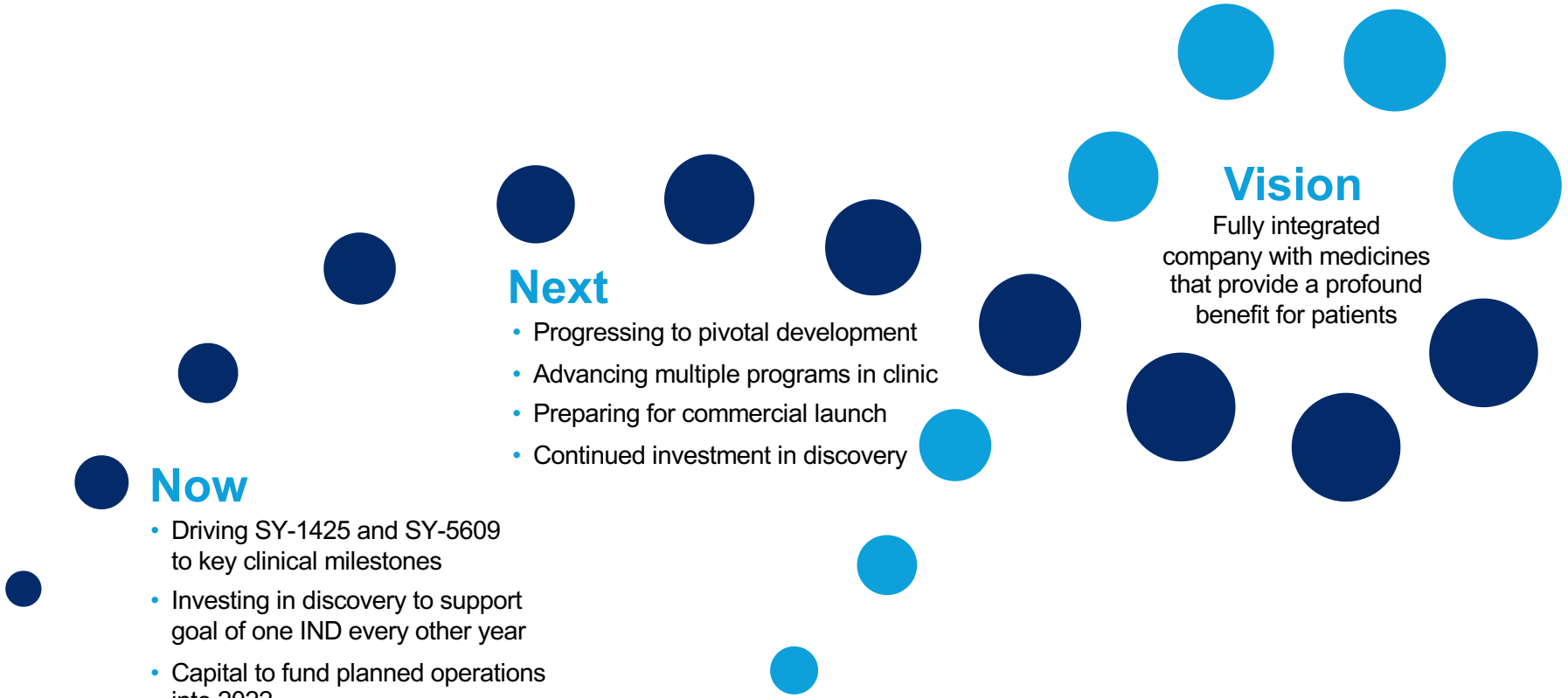
- Option to obtain exclusive worldwide license to products resulting from the collaboration
- Responsible for clinical development, manufacturing and commercialization

Milestones expected in 2020 and 2021

SY-1425	Potential POC in relapsed or refractory AML	**Q4 2020**
	Mature data in newly diagnosed unfit AML	**Q4 2020**
SY-5609	Initiate Phase 1 trial	✓
	Initial safety, tolerability and PK/PD data	**Q4 2020**
	Additional dose escalation data, including clinical activity	**mid-2021**
Discovery	Name next development candidate	**end 2021**
	Robust early-stage pipeline development	**Ongoing**

SYROS

Rapidly advancing toward our vision



Now

- Driving SY-1425 and SY-5609 to key clinical milestones
- Investing in discovery to support goal of one IND every other year
- Capital to fund planned operations into 2022

Next

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

Vision

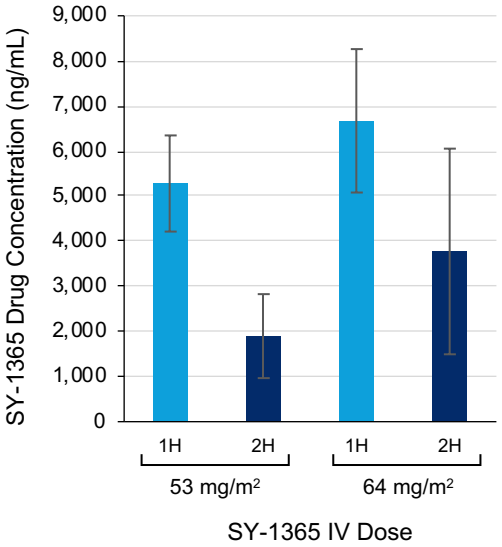
Fully integrated company with medicines that provide a profound benefit for patients

SYROS

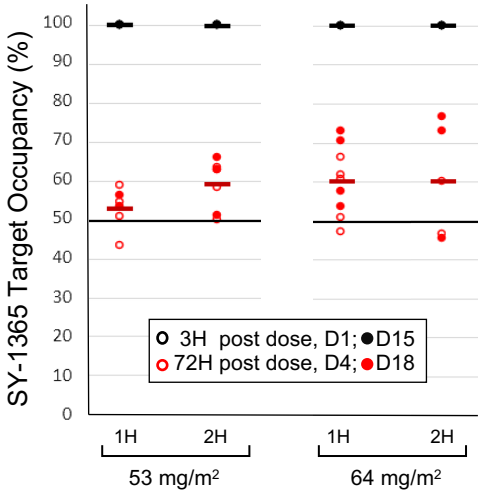
Appendix

Peri-infusional AEs in Phase 1 trial were associated with peak blood SY-1365 concentrations and not CDK7 target engagement

SY-1365 Plasma Cmax



SY-1365 Target Engagement



Infusion-associated Adverse Events (≥ 20%)*

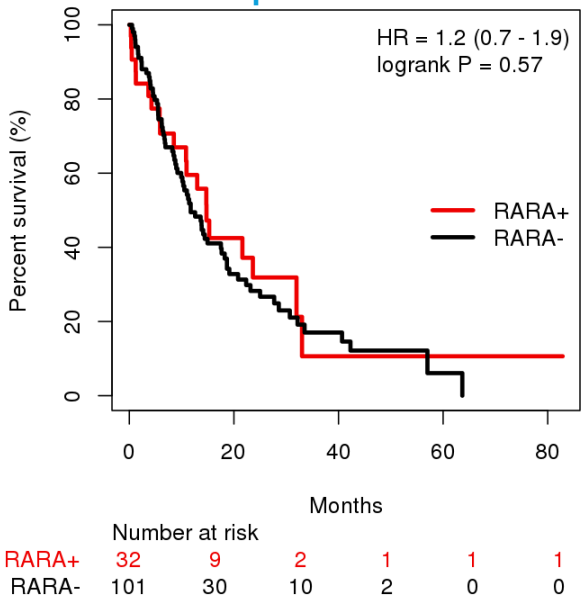
Preferred Term	All Grades n (%)		≥ Grade 3 n (%)	
	N = 31	N = 24	N = 31	N = 24
	1 hour	2 hour	1 hour	2 hour
Headache	19 (61)	12 (50)	2 (6)	0 (0)
Nausea	12 (39)	5 (21)	1 (3)	0 (0)
Vomiting	10 (32)	1 (4)	1 (3)	0 (0)

*Includes AEs experienced in patients treated with 53 mg/m² and 64 mg/m²

Longer infusions maintained CDK7 target engagement while lowering peak drug concentrations and decreasing frequency and severity of peri-infusional AEs

RARA is not a prognostic biomarker in AML patients

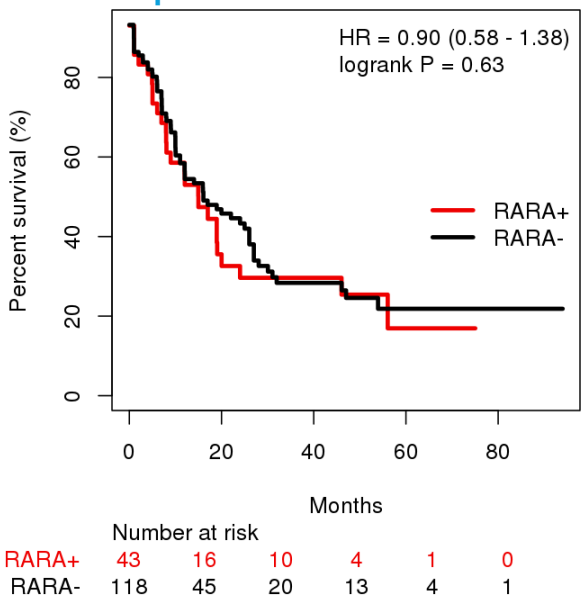
Analysis of BeatAML Registry RARA expression and survival[1]



Number at risk

RARA+	32	9	2	1	1	1
RARA-	101	30	10	2	0	0

Analysis of TCGA RARA expression and survival[2]



Number at risk

RARA+	43	16	10	4	1	0
RARA-	118	45	20	13	4	1

- Independent analyses of BeatAML[1], TCGA[2], and AML patient sample analyses[3] show that prognosis is similar regardless of levels of RARα expression

[1] Tyner et al., Functional Genomic Landscape of Acute Myeloid Leukaemia, Nature 2018
[2] TCGA Research Network, Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia, NEJM 2013; Expression and survival data from PanCancerAtlas portal on GDC: https://gdc.cancer.gov/about-data/publications/pancanatlas
[3] McKeown et al., Superenhancer Analysis Defines Novel Epigenomic Subtypes of Non-APL AML, Including an RARα Dependency Targetable by SY-1425, a Potent and Selective RARα Agonist, Cancer Discovery 2017

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