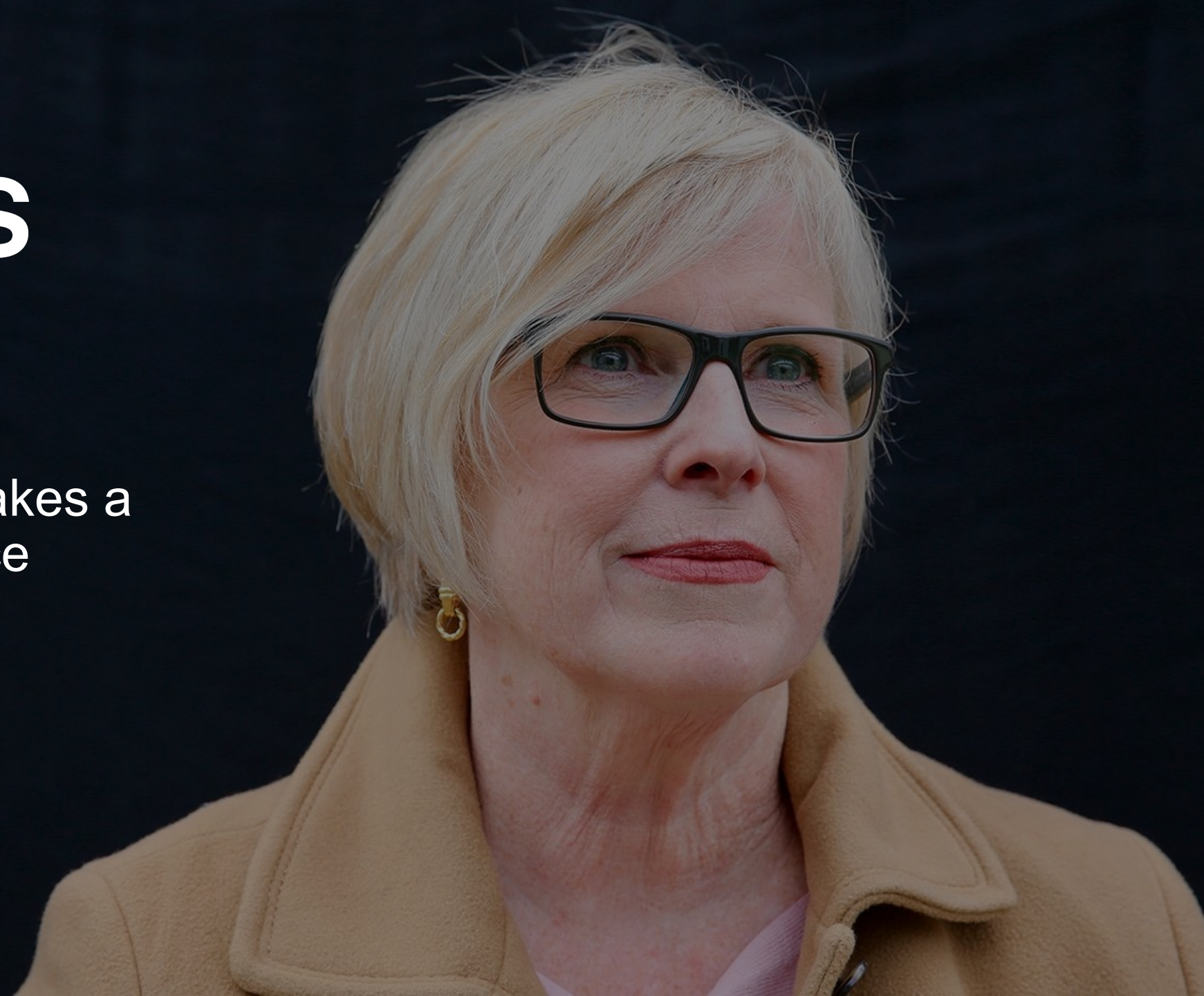
SYROS

An Expression Makes a World of Difference

August 2021



Forward-looking statements

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

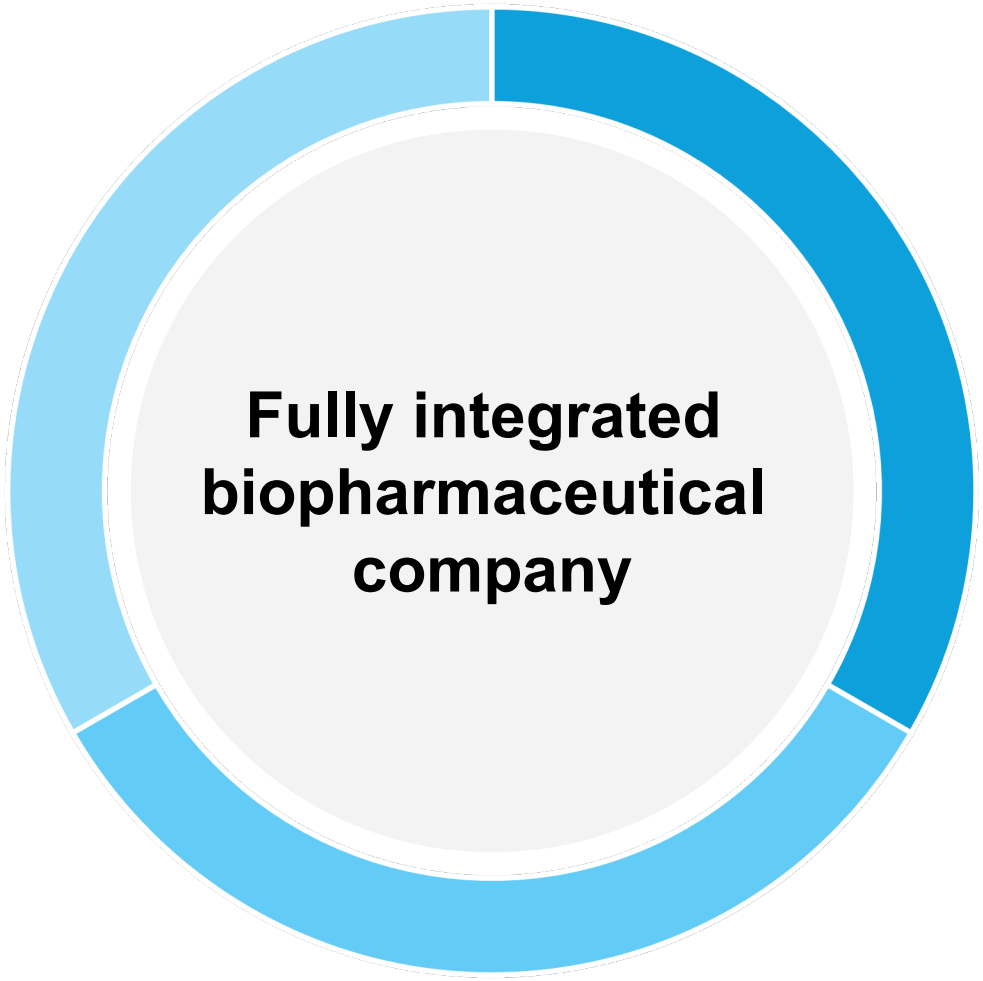
We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including our ability to: advance the development of our programs, including tamibarotene (formerly SY-1425), SY-2101 and SY-5609, under the timelines we project in current and future clinical trials; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of our drug candidates; replicate scientific and non-clinical data in clinical trials; successfully develop a companion diagnostic test to identify patients with the RARA biomarker; obtain and maintain patent protection for our drug candidates and the freedom to operate under third party intellectual property; obtain and maintain necessary regulatory approvals; identify, enter into and maintain collaboration agreements with third parties, including our ability to perform under our collaboration agreements with Incyte Corporation and Global Blood Therapeutics; manage competition; manage expenses; raise the substantial additional capital needed to achieve our business objectives; attract and retain qualified personnel; and successfully execute on our business strategies; risks described under the caption “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2020 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, each of which is on file with the Securities and Exchange Commission (SEC); and risks described in other filings that we may make with the SEC in the future.

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

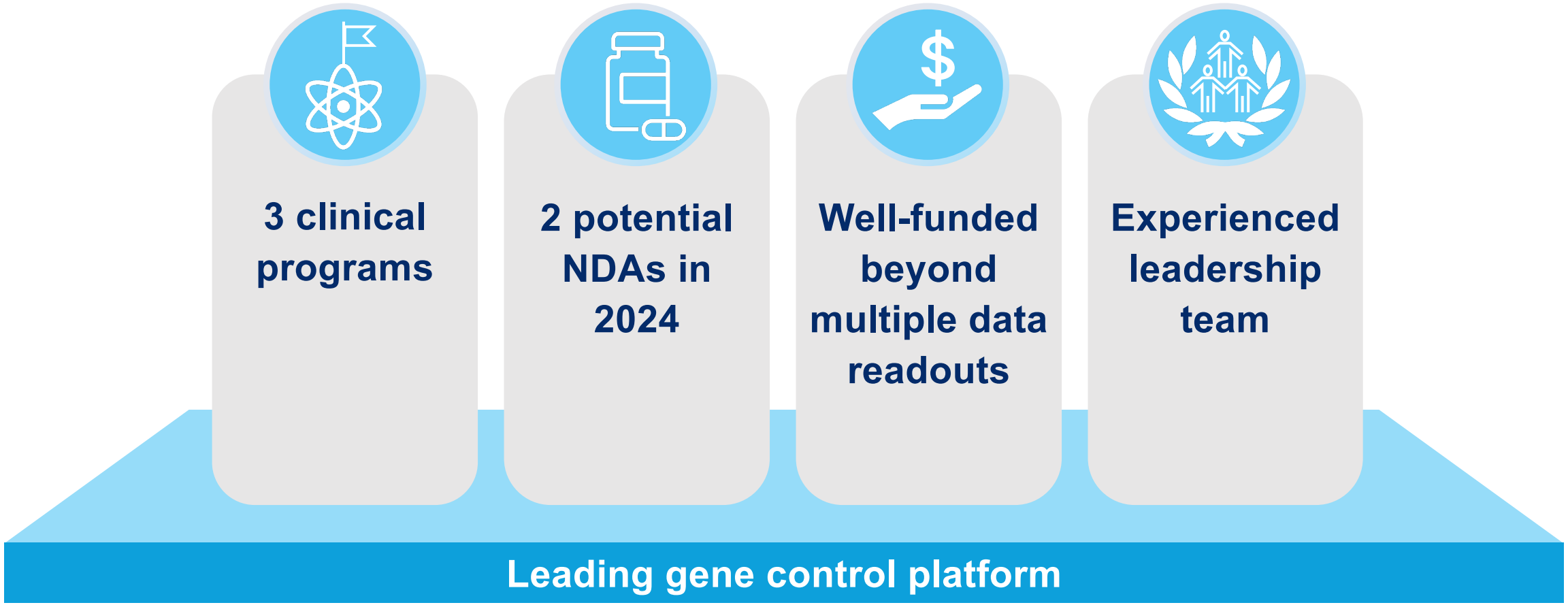
Any forward-looking statements contained in this presentation speak only as of the date this presentation is made, and we expressly disclaim any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

Accelerating our vision

- Targeted hematology therapy franchise
- Selective CDK inhibitor franchise
- Gene control discovery engine



Rapidly advancing toward being a commercial-stage company



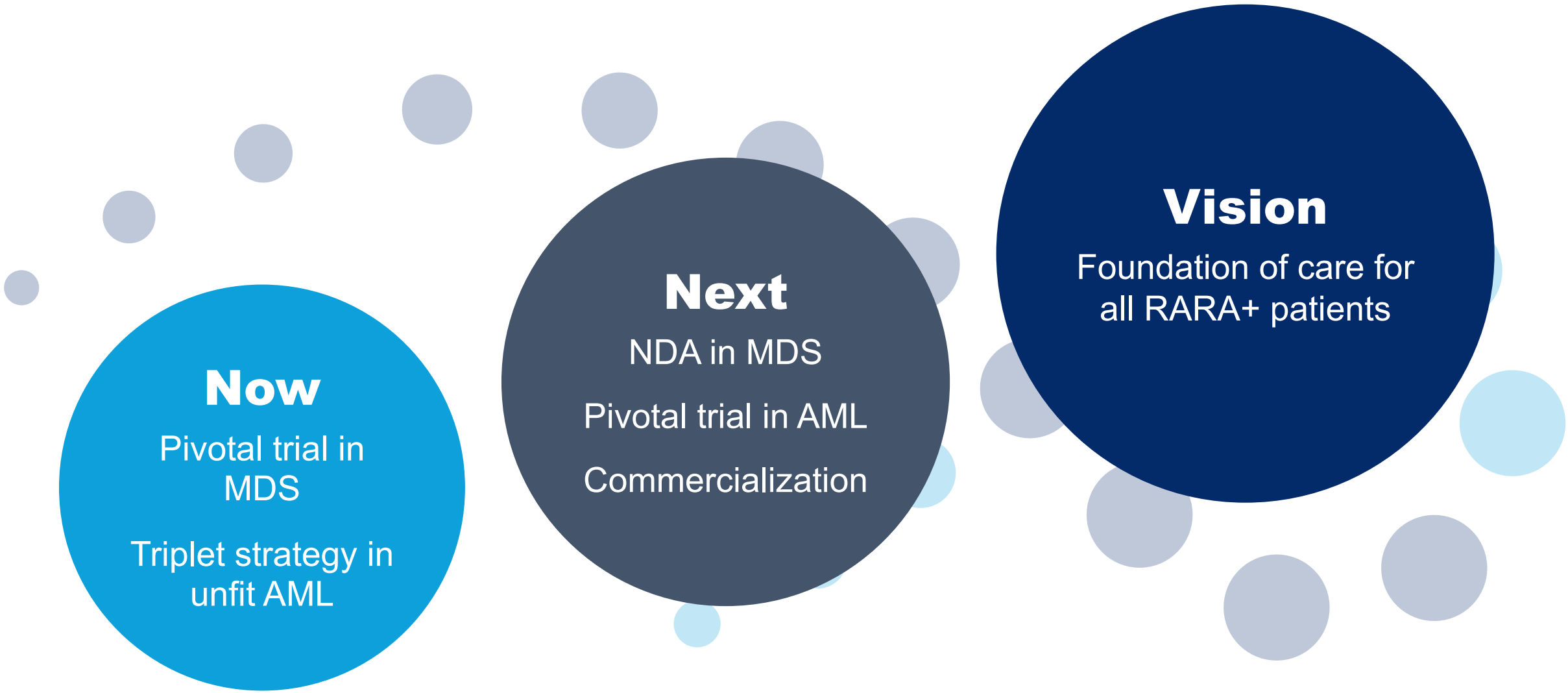
Advancing a growing clinical-stage pipeline for targeted patient populations

Program	Indication	Early Clinical	Mid-Clinical	Pivotal	Commercial Rights
Tamibarotene (oral RARα agonist)	Newly diagnosed HR-MDS (w/aza)	SELECT-MDS-1 Trial			SYROS Americas, Europe, Australia, Israel & Russia
	Newly diagnosed unfit AML (w/ven+aza)		Ph2 2H2021		
SY-2101 (oral ATO)	Newly diagnosed APL (w/ATRA)		Dose confirm 2H2021; Ph3 2022		SYROS
SY-5609 (oral CDK7 inhibitor)	Select solid tumors		Expansion 2H2021		SYROS

Tamibarotene is approved in Japan as Amnolake® for patients with relapsed/refractory APL

Tamibarotene (formerly SY-1425)
Selective oral RARα agonist

Clear vision for tamibarotene in RARA-positive cancers



Compelling data and clear path forward for tamibarotene

Strong rationale in targeted subset

~ 30% of MDS and AML patients RARA+

Tamibarotene/aza induces high CR rates, rapid onset of action and meaningful durability in RARA+ ND unfit AML[1]

Tamibarotene safety profile supports multiple combination opportunities

New translational data suggest RARA biomarker selects for AML patients who may be less likely to benefit from ven[2]

HR-MDS is closely related to AML with opportunity to set new standard of care

SELECT-MDS-1 (Phase 3) trial w/ aza in RARA+ ND HR-MDS

SELECT-AML-1 (Randomized Phase 2) trial with ven/aza in RARA+ ND unfit AML

[1]de Botton, ASH 2020; [2]Fiore, ASH 2020

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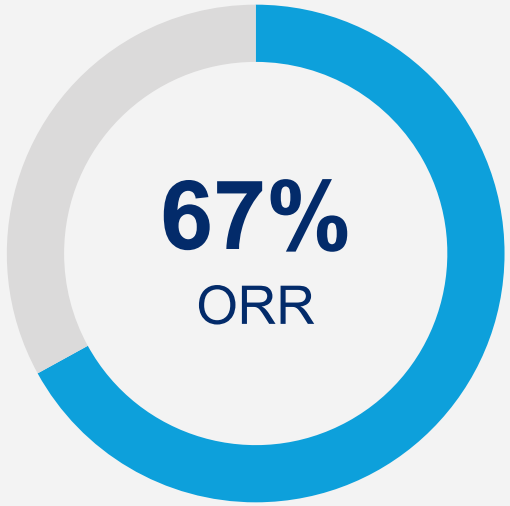
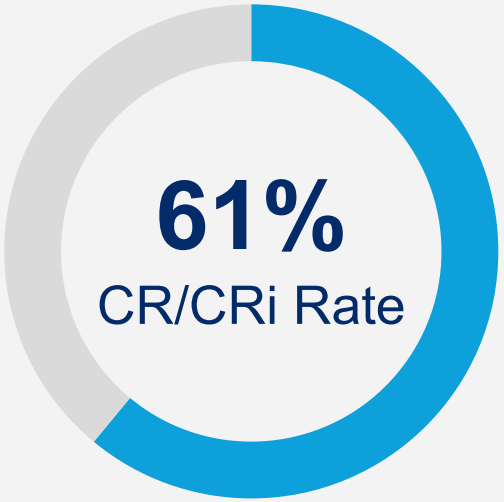
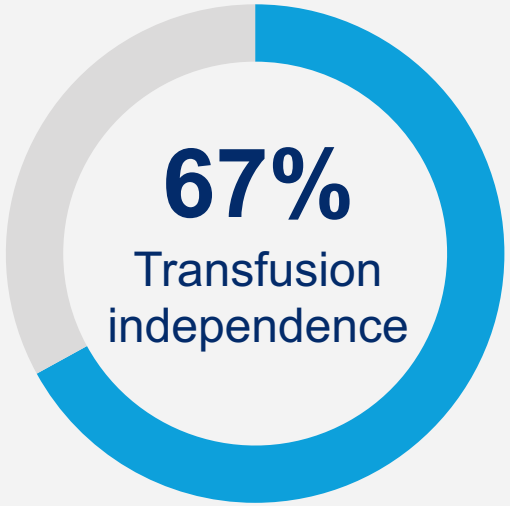
High CR rates, rapid onset of action, and clinically meaningful durability in RARA-positive ND unfit AML







1.2 months
Time to response

10.8 months
Duration of response

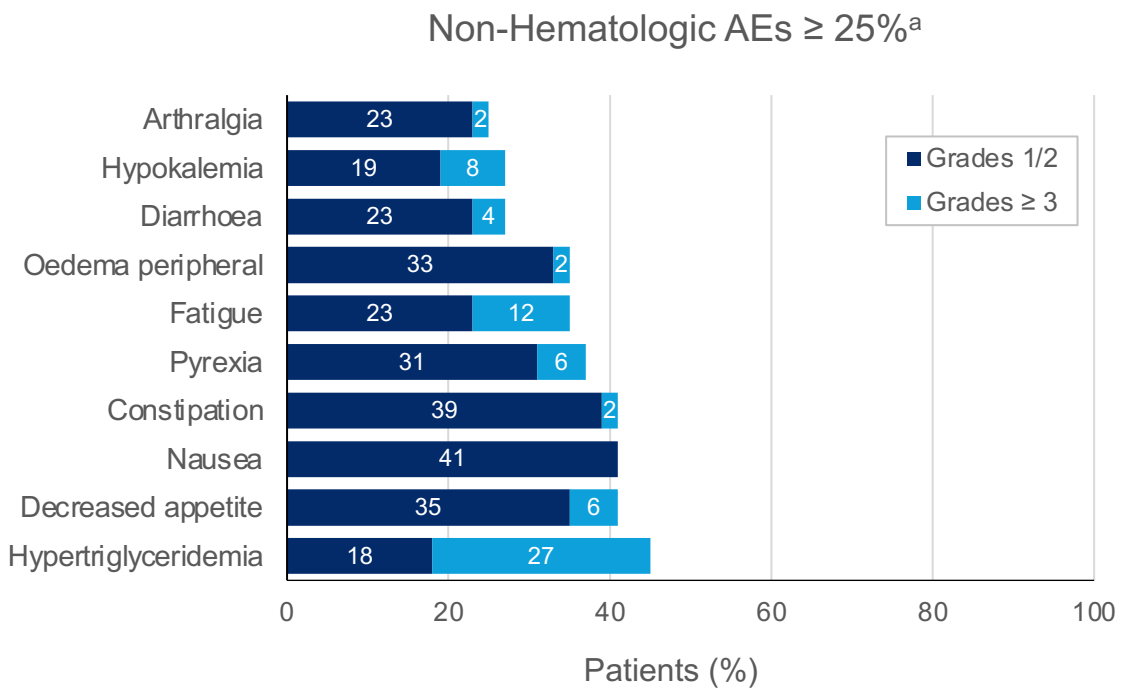
18 months
Overall survival for complete responders

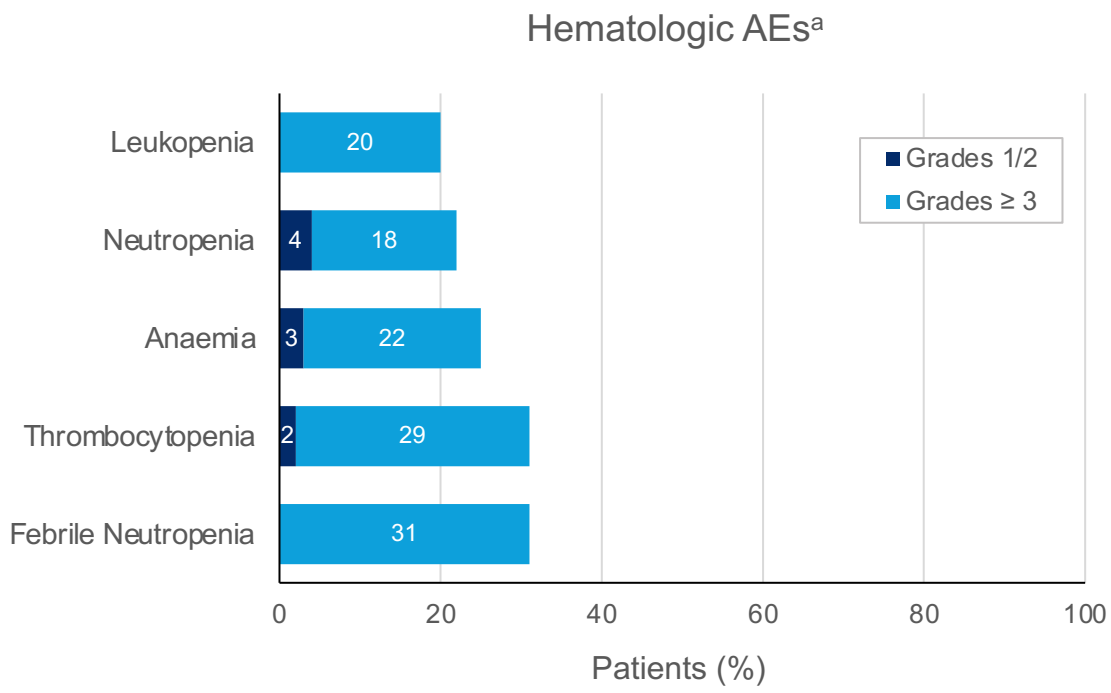
- 89% of CRs were deep molecular or cytogenetic CRs
- Responses seen irrespective of mutation or cytogenetic risk
- Response rates in RARA-negative patients comparable to historical rates for single-agent aza[1-3]

Data from 18 response evaluable RARA-positive and 28 response evaluable RARA-negative patients presented at ASH 2020 meeting

[1]Dombret, Blood 2015; [2]Fenaux, JCO 2010; [3]Thepot, American Journal of Hematology 2014

Generally well-tolerated combination in ND unfit AML patients





- No increase in neutropenia, anemia and thrombocytopenia compared to single-agent aza
- Majority of non-hematologic AEs are low grade and reversible

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

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ND HR-MDS represents ideal opportunity for tamibarotene in combination with azacitidine

HR-MDS is closely related to AML

- HR-MDS and AML on a disease continuum; distinguished by % blasts in marrow
- More than half of patients progress to AML[1]
- Neutropenia may lead to infection-related complications, including death[2]

Opportunity to set new standards of care

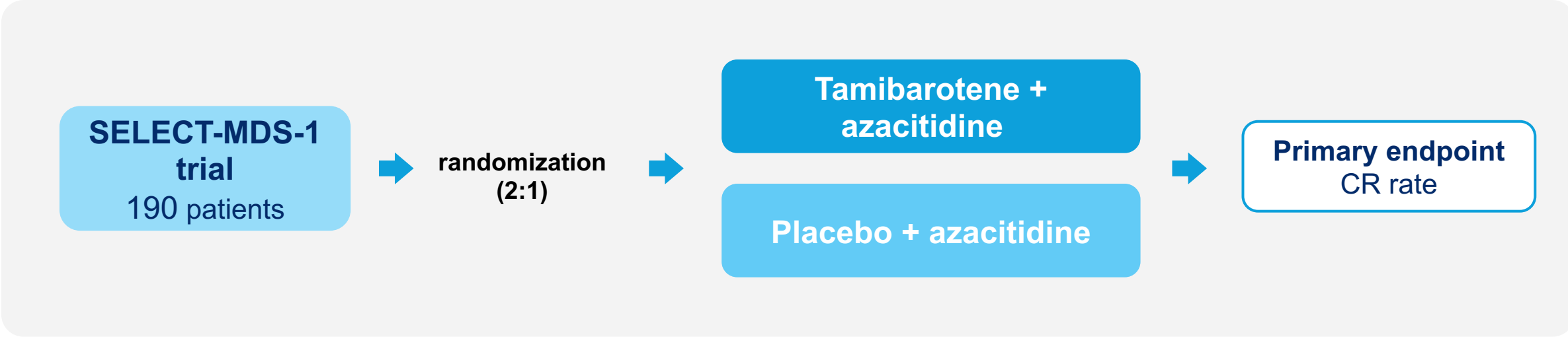
- HMAs are only approved agents
- Low CR rates ranging from 5-25%, with OS estimated between 15-25 months[1, 3-4]
- Only 45% of patients achieve transfusion independence[3]

Our data suggest strong potential for tamibarotene in MDS

- 60% (n=5) response-evaluable RARA+ R/R HR-MDS patients achieved hematologic responses with single agent tamibarotene
- 67% (n=6) of response-evaluable RARA+ low blast count AML patients achieved CR with tamibarotene/aza
  - 27% (n=11) of response-evaluable RARA-negative low blast count AML patients achieved CR
- No additive neutropenia/anemia

[1]Greenberg, Blood 2012; [2]Toma, Haematologica 2012; [3]VIDAZA (azacitidine) USPI; [4]DACOGEN (deitabine) USPI

Ongoing placebo-controlled SELECT-MDS-1 (Phase 3) trial in RARA-positive ND HR-MDS



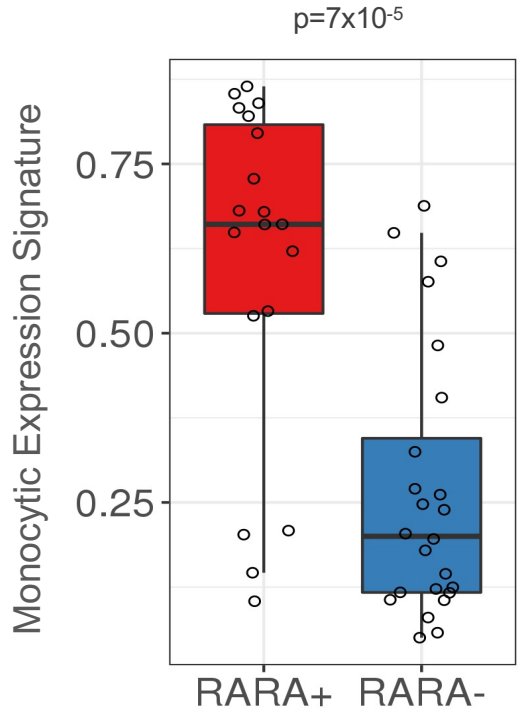
- Robustly designed, double-blind, placebo-controlled study
- 90% power to detect a difference in CR rates between experimental and control arms
- 2:1 randomization with one-sided alpha of 0.025
- FDA feedback supports:
  - Focus on RARA+ population
  - CR as primary endpoint for accelerated/full approval
  - Azacitidine as appropriate comparator

Key Milestones

Trial initiated	1Q 2021
Potential NDA	2024

New translational data support the potential for the RARA biomarker to enrich for patients who may be less likely to benefit from standard of care

Analysis of Tamibarotene Trial Patient Samples



- 30% of patients do not respond to upfront treatment with ven/aza and a small number of patients have long-term remissions
- Venetoclax resistance associated with monocytic phenotype,[1-3] which includes low BCL2 and high MCL-1 expression
- Most RARA+ patients, including those who achieved CR/CRi in tamibarotene trial, have this monocytic phenotype[4]

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

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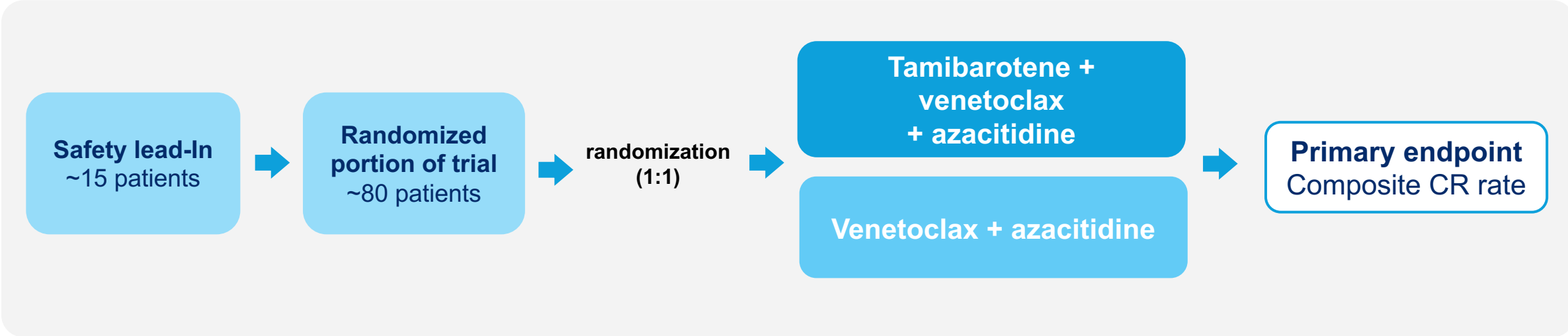
Initiating SELECT-AML-1 (Randomized Phase 2) trial of triplet regimen in ND RARA-positive unfit AML patients



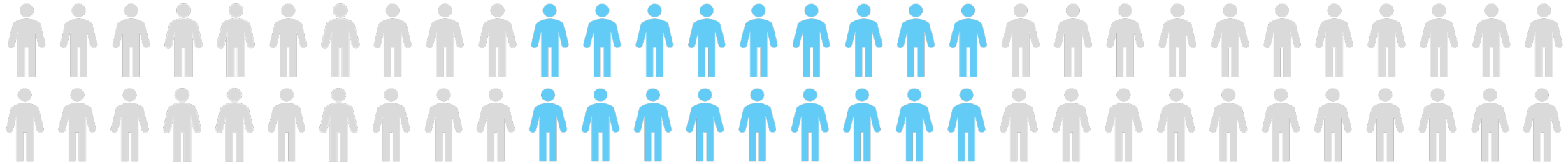
Plan to also evaluate triplet as salvage strategy for patients in control arm who don't respond to ven/aza

Key Milestones

Initiate SELECT-AML-1 trial	2H 2021
Initial data from SELECT-AML-1 trial	2022

ND HR-MDS and unfit AML represent significant market opportunities

~30% of all AML and MDS patients are RARA-positive



Newly diagnosed HR-MDS

- ~15,000 new cases annually in US and EU
- Expected to grow into $1B+ market
- No new approved agents, aside from HMAs, in a decade
- Existing options offer limited efficacy

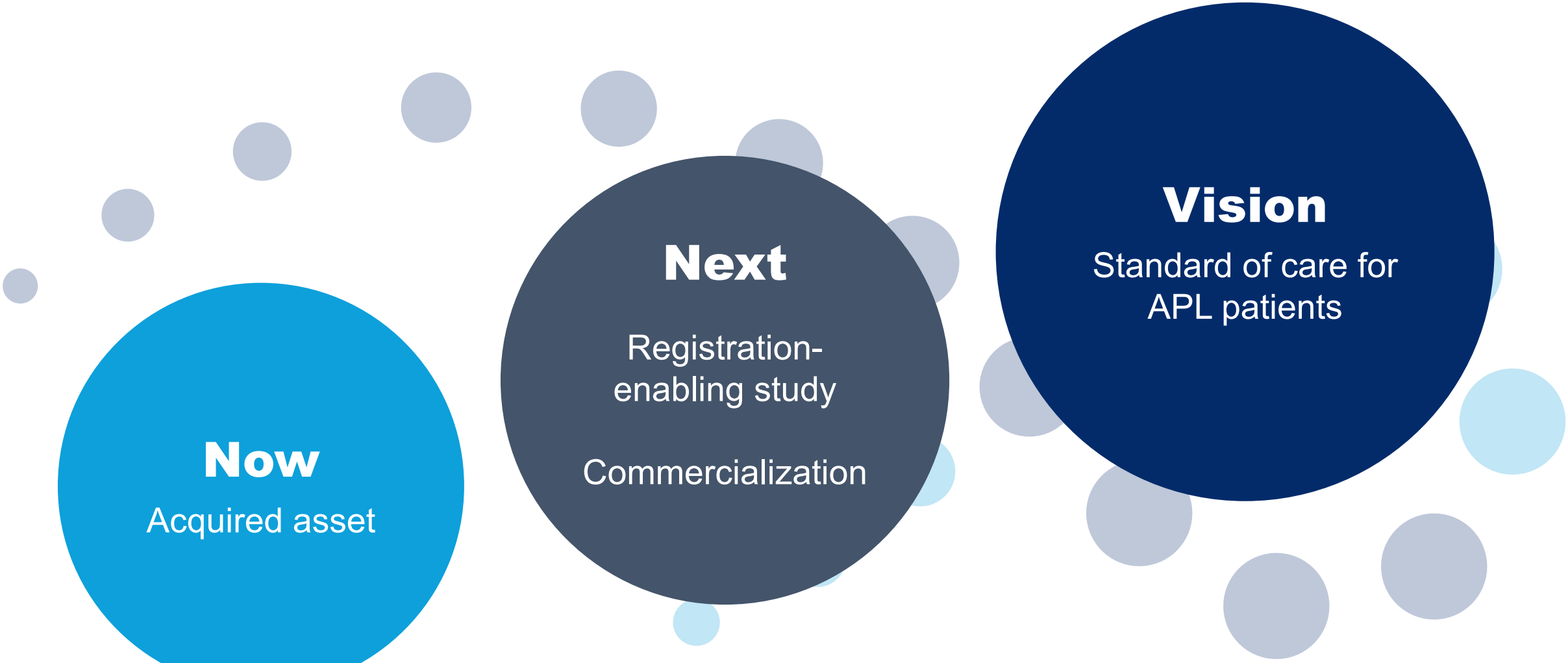
Newly diagnosed unfit AML

- Over 18,000 new cases annually in US and EU
- Expected to grow into $2B+ market
- ~1/3 of patients don't respond to SOC ven/aza and have poor prognosis and a small number of patients have long-term remissions

Sources: Epidiemology and Sales projections from DRG Myelodysplastic Syndromes-Landscape & Forecast-Report 2020 and from DRG Acute Myelogenous Leukemia-Landscape & Forecast-Report 2020; Prevalence of RARA-positive patients based on data presented at ESH 2017 and ESH 2019; Resistant Ven population - Dinardo, NEJM 2020; Dinardo, Blood 2019

SY-2101
Novel oral form of arsenic trioxide

Our vision for SY-2101

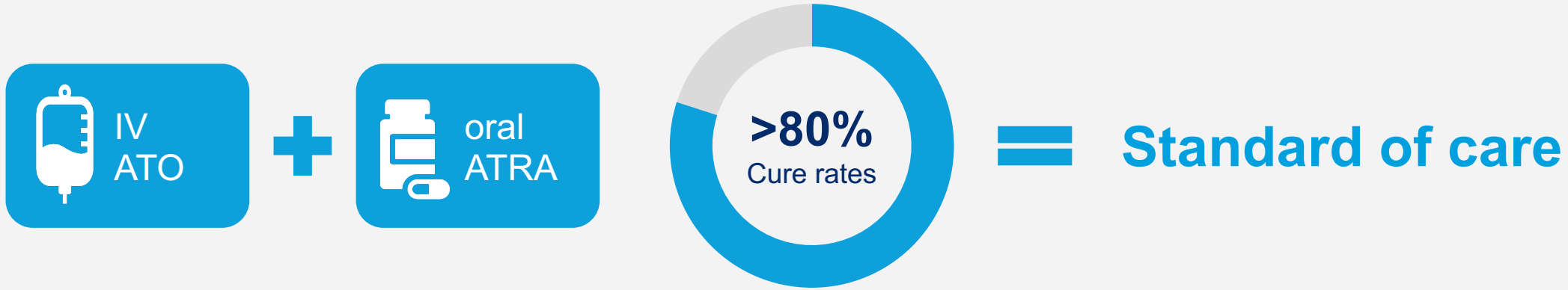


SY-2101: Highly synergistic with our advancing targeted heme franchise

- Strategic opportunity as we accelerate toward becoming a commercial-stage company
- Potential to become standard of care in APL
  - Novel oral capsule of arsenic trioxide (ATO)
- Clinical-stage asset with opportunity for accelerated approval based on molecular CR
  - Potential NDA filing in 2024
- Orphan drug designation granted in US and EU
- Issued patents provide opportunity to extend exclusivity

Capitalizes on our expertise to build a leadership position in targeted therapies for hematologic disorders

IV ATO is transformative therapy for APL patients but comes with heavy treatment burden



- Current course of treatment involves up to 140 two- to four-hour infusions over nearly a year
  - Induction – up to 60 days of daily infusions until CR is achieved
  - Consolidation – 80 days of 5 days/week for 4 weeks/cycle for 4 cycles/treatment course

Significant opportunity to reduce treatment burden, increase access and reduce health care costs and utilization

NCCN AML treatment guidelines (Nov 2020)
Trisenox (arsenic trioxide) USPI

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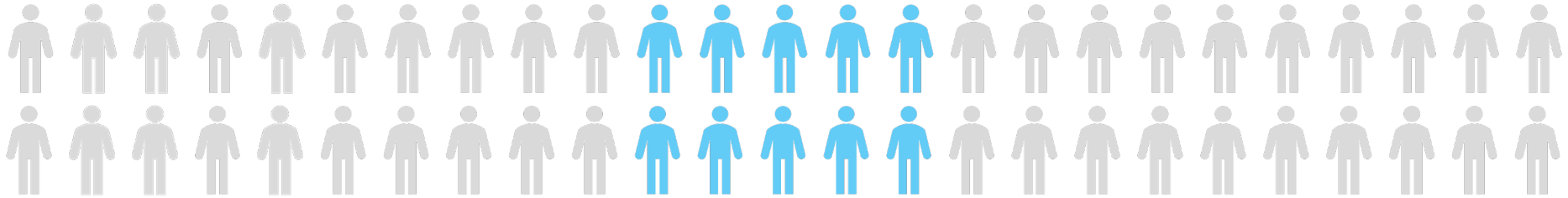
Opportunity for SY-2101 to become standard of care in significant market

APL is ~10 % of AML



Newly diagnosed APL

- Genetic fusion of RARA and PML genes
- ~2,000 patients diagnosed in US and Europe annually[1,2]
- ~$250 million overall market opportunity based on current pricing for IV ATO[3]
- Opportunity to become the standard of care and be served with targeted sales force

[1]Tallman 2008 Semin Hematol
[2]NCI Surveillance, Epidemiology and End Results Program – 2020 Acute Myeloid Leukemia
[3]IBM Truven Redbook pricing for Trisenox

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Completed Phase 1 PK study of SY-2101

Dosing	Three dosing cohorts: 5, 10 and 15 mg orally Once daily
Patient population	12 patients with advanced hematologic malignancies Median age: 76.5 Prior lines of therapy: Up to 5
Safety	Generally well-tolerated with low-grade AEs Lower adverse events in liver enzymes (8.3%) compared to IV ATO (~44%) Lower QTc prolongation (8.3%) compared to IV ATO (25%)
Pharmacokinetics	Good bioavailability, with generally dose proportional PK Achieves exposure levels (AUC and Cmax) in range of approved IV ATO dose

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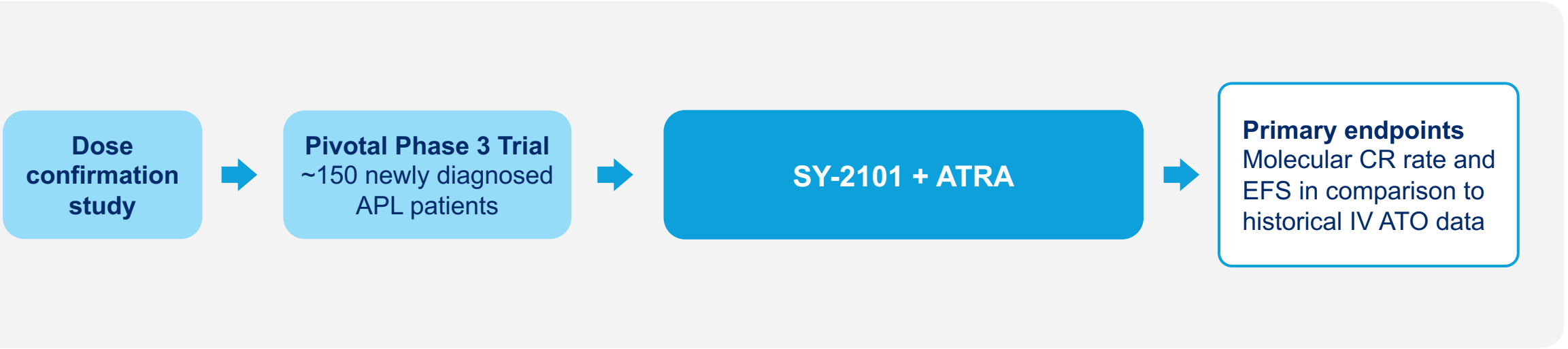
Ravandi et al 2020 *Haematologica*
Trisenox (arsenic trioxide) USPI

Advancing SY-2101 toward registration-enabling Phase 3 trial



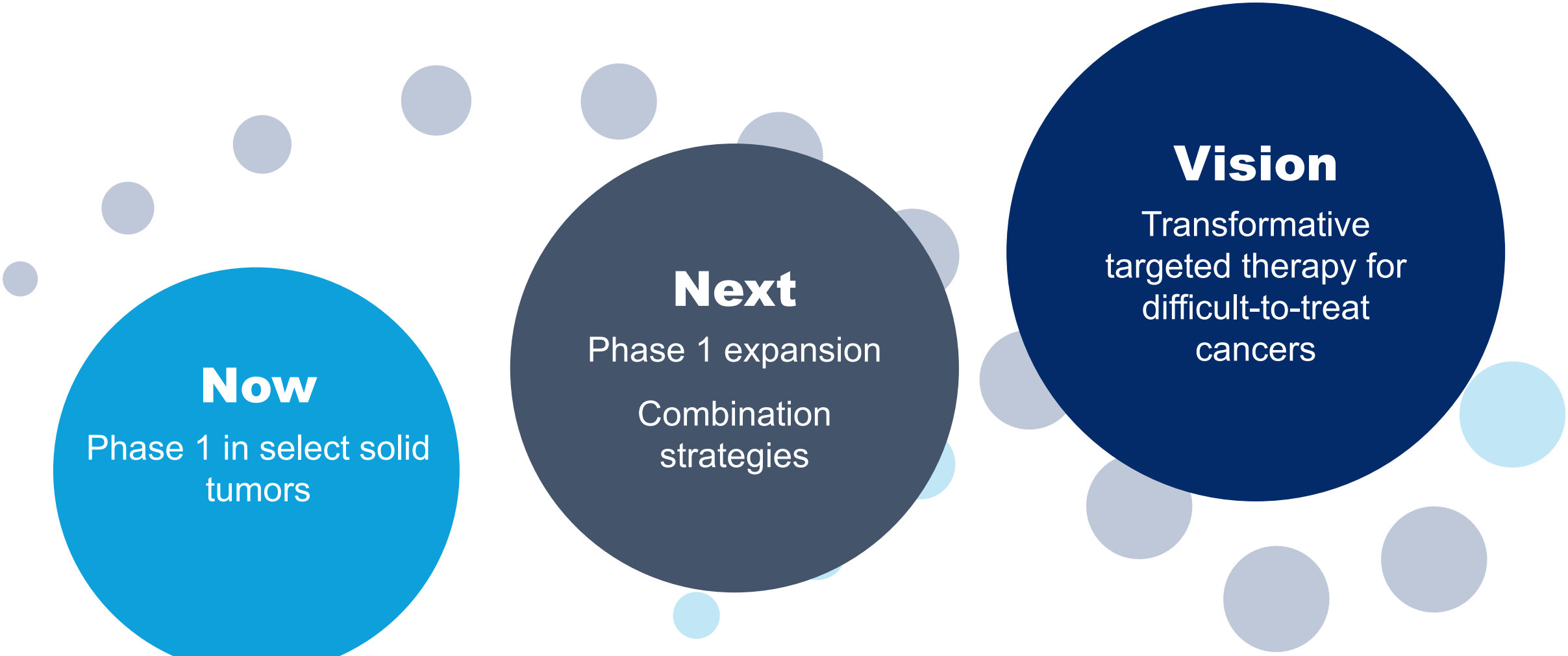
- FDA feedback supports:
  - Molecular CR as primary endpoint for accelerated approval
  - Event-free survival (EFS) as primary endpoint for full approval

Key Milestones

Initiate dose confirmation study	2H 2021
Confirmatory dose/PK data	1H 2022
Initiate Phase 3	2022
Potential NDA	2024

SY-5609
Selective oral CDK7 inhibitor

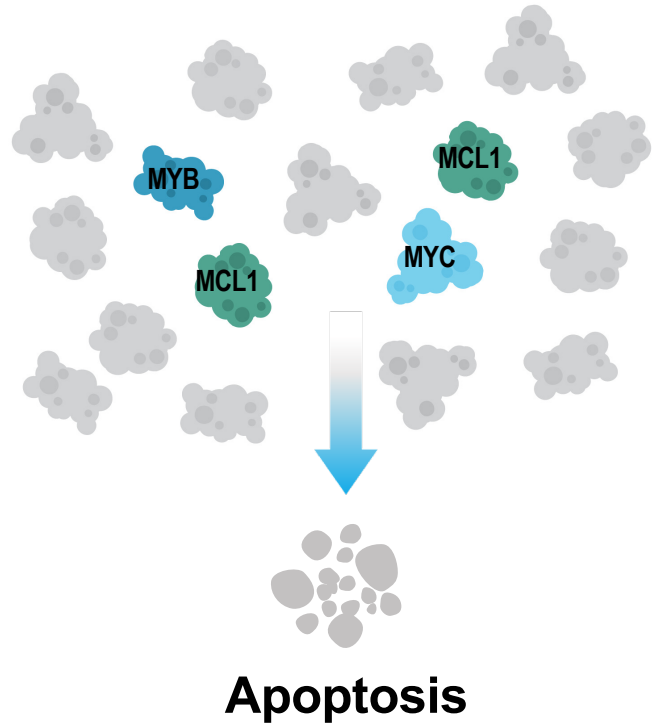
Our vision for SY-5609



Selective CDK7 inhibition attacks two fundamental processes in cancer

Transcription

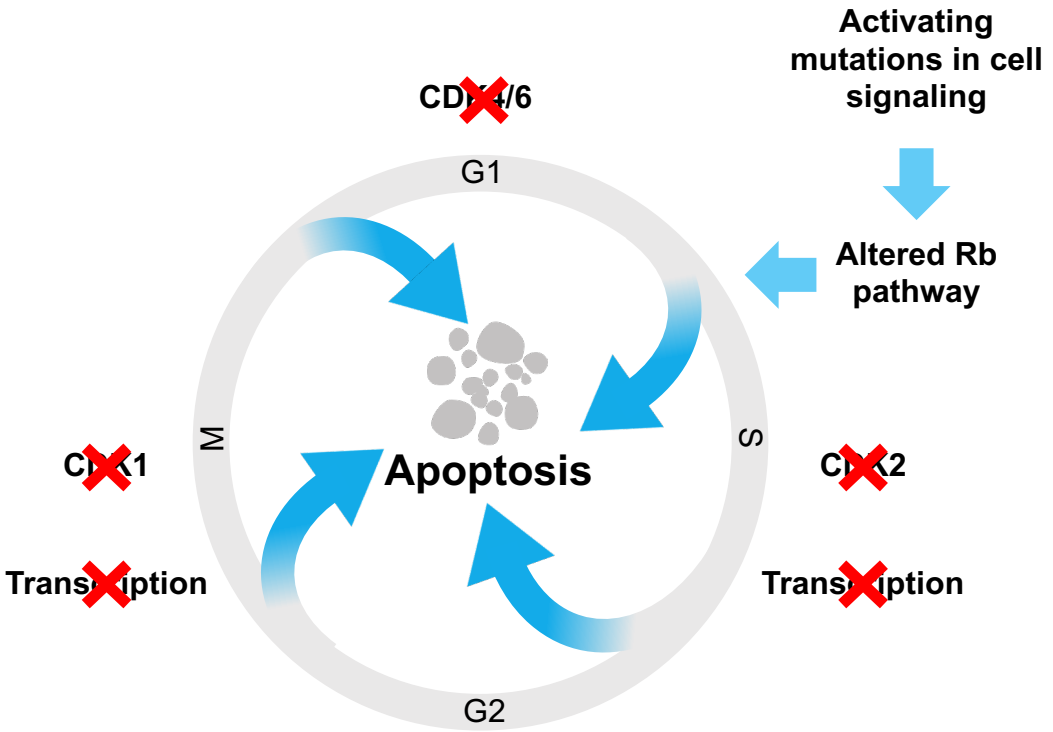
CDK7i has been shown preclinically to decrease expression of these transcription factors and proteins



CDK7i

Cell Cycle

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



Development strategy to maximize potential of SY-5609

Compelling preclinical data

+

Strong mechanistic rationale

+

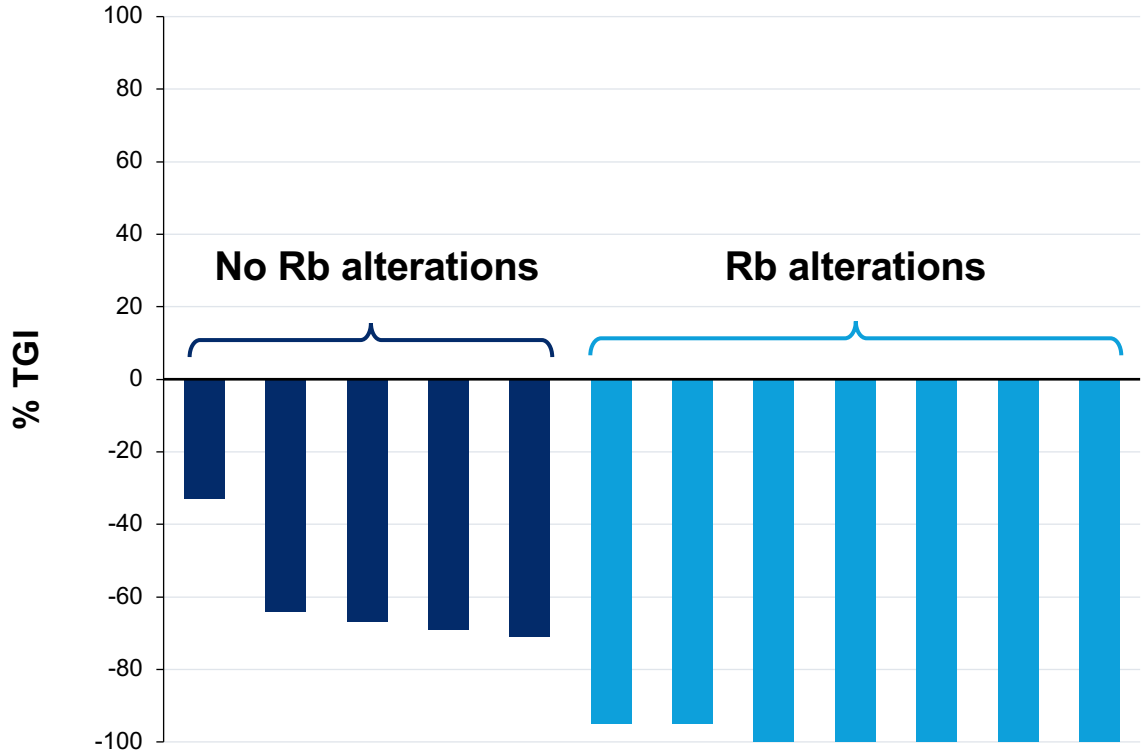
High unmet need

→ Leveraging Rb pathway alterations

→ Exploiting transcriptional and cell cycle dependencies

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

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



Supports 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]

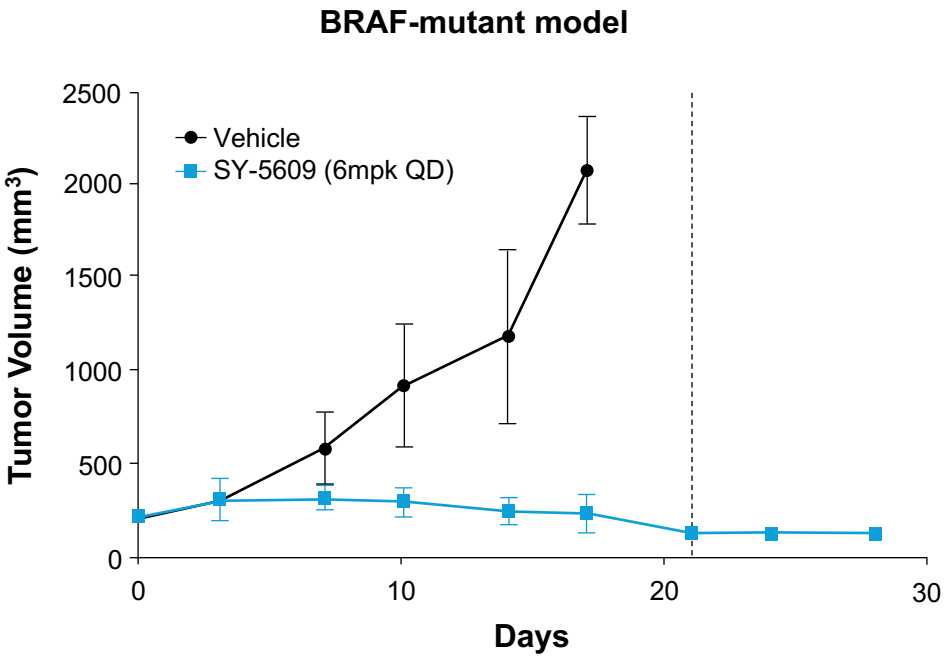
75-90% of small cell lung cancer patients[3]

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

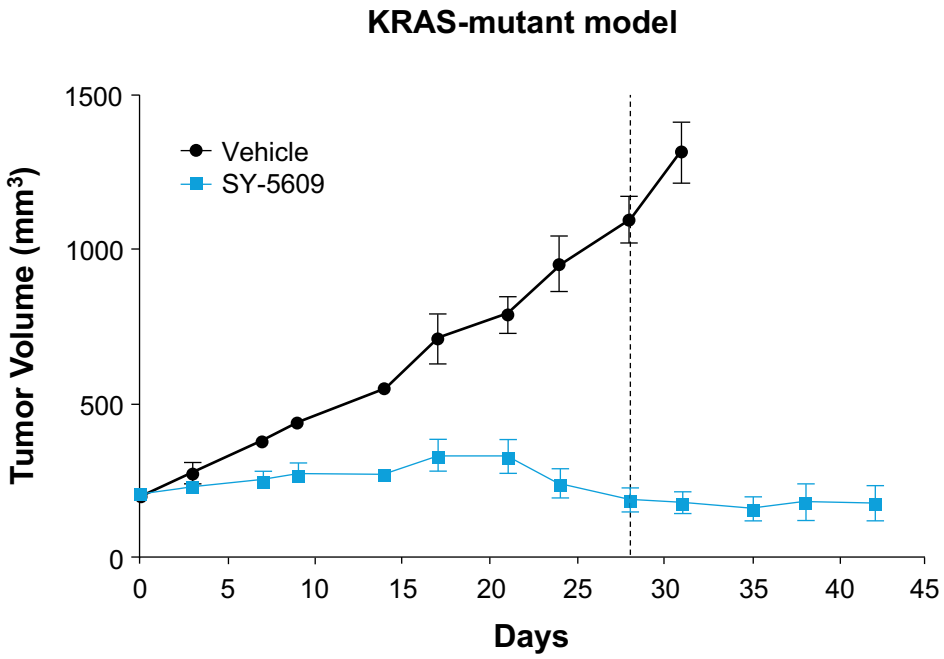
Targeting dependencies on transcription and cell cycle control induces robust responses in preclinical colorectal and pancreatic cancer models

Colorectal Cancer



- 67% (20/30) of models demonstrated ≥ 50% TGI
- 23% (7/30) demonstrated deep responses of ≥ 90% TGI
- Deep responses enriched in BRAF-mutant (5/10) models

Pancreatic Cancer



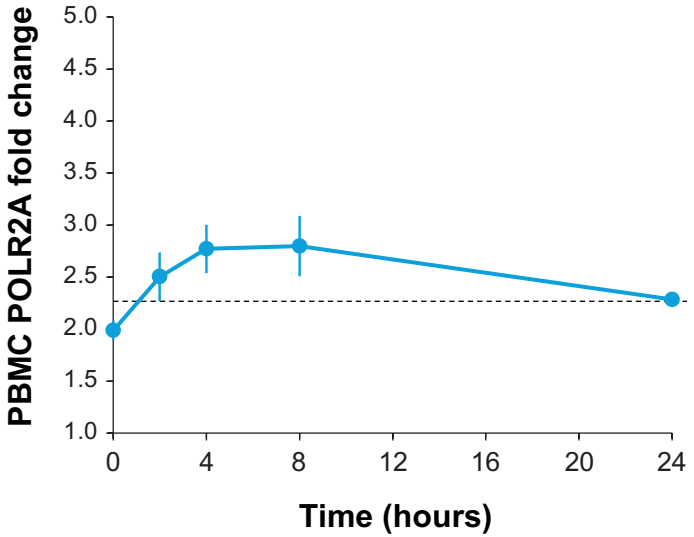
- 75% (6/8) of models demonstrated ≥50% TGI
- Regressions seen in 50% (4/8) of models
- Responses observed in CDKN2A-mutant and non-mutant and TP53-mutant and non-mutant models

CRC data presented in May 2020 at ASCO Virtual Symposium; pancreatic cancer data is internal company data

SY-5609 induced biological activity associated with tumor regressions in preclinical models and clinical activity with first-generation CDKi

POLR2A PD vs Time

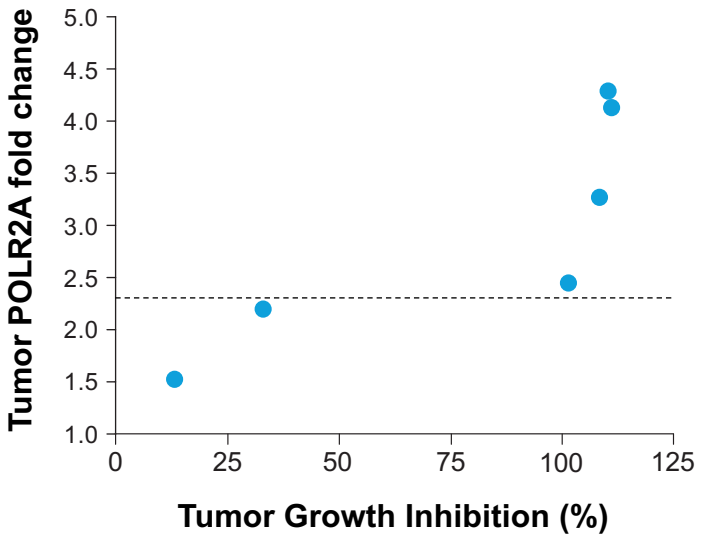
SY-5609-101 PBMCs



- POLR2A fold-change measured at steady state (day 15) with 3 mg continuous daily dosing

POLR2A PD vs Tumor Growth Inhibition

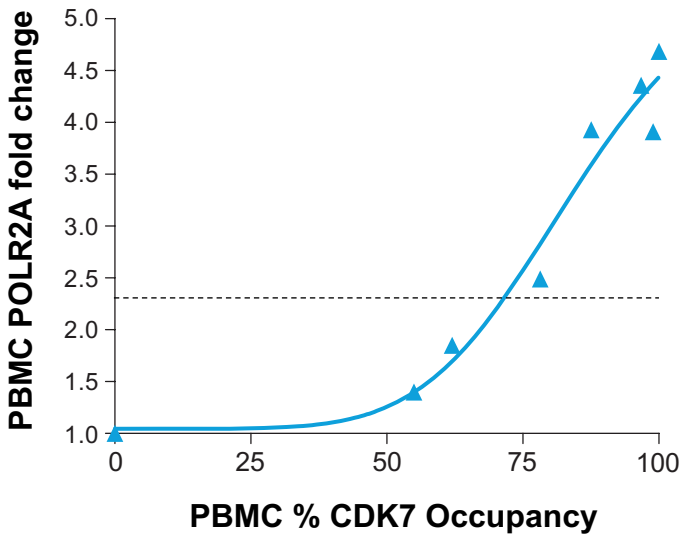
SY-5609 CRC PDX



- POLR2A fold-change measured at trough (24h) after single dose
- Tumor growth inhibition measured at end of 28 day cycle (cycle = SY-5609 qdx21d, 7d off)

POLR2A PD vs CDK7 Occupancy

SY-1365-101 PBMCs



- POLR2A fold-change similar between PBMCs and tumor biopsies

- AEs predominantly low grade; most frequent related AEs include nausea, diarrhea, fatigue, platelet count decrease and vomiting

Ongoing Phase 1 dose escalation trial in select solid tumors

Ongoing dose escalation

Single agent

Advanced solid tumors → Multiple doses and intermittent schedules

Plans for Expansion

Further explore SY-5609 as single and combination agent

- Advanced solid tumor populations include – breast, colorectal, lung, ovarian, pancreatic, and tumors with Rb alterations
- Established MTD for continuous daily dosing

Key Milestones

Additional Dose Escalation Data	ESMO 2021
Expansion phase of Phase 1 trial	2H 2021

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Agreement with Roche to evaluate potential of SY-5609 with immunotherapy in BRAF-mutant colorectal cancer in Phase 1/1b trial

Strategic rationale for evaluating SY-5609 with Roche's atezolizumab, a PD-L1 inhibitor

- First clinical investigation of a CDK7 inhibitor with an immunotherapy
- Supported by strong mechanistic rationale and translational data
  - Preclinical data show CDK7 inhibition induces DNA replication stress and genome instability in cancer cells, triggering immune-response signaling[1]
  - In animal models, CDK7 inhibition enhances tumor response to anti PD1 immunotherapy, prolonging overall survival, and increasing immune cell infiltrates[1]
  - Our preclinical data show that SY-5609 induced dose-dependent tumor growth inhibition at well-tolerated doses in colorectal cancer models. Deeper responses were observed more frequently in models with BRAF mutations relative to wild-type models[2]

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[1]Zhang et al., 2020, Cancer Cell 37, 1-18; [2]Data presented at ASCO 2020

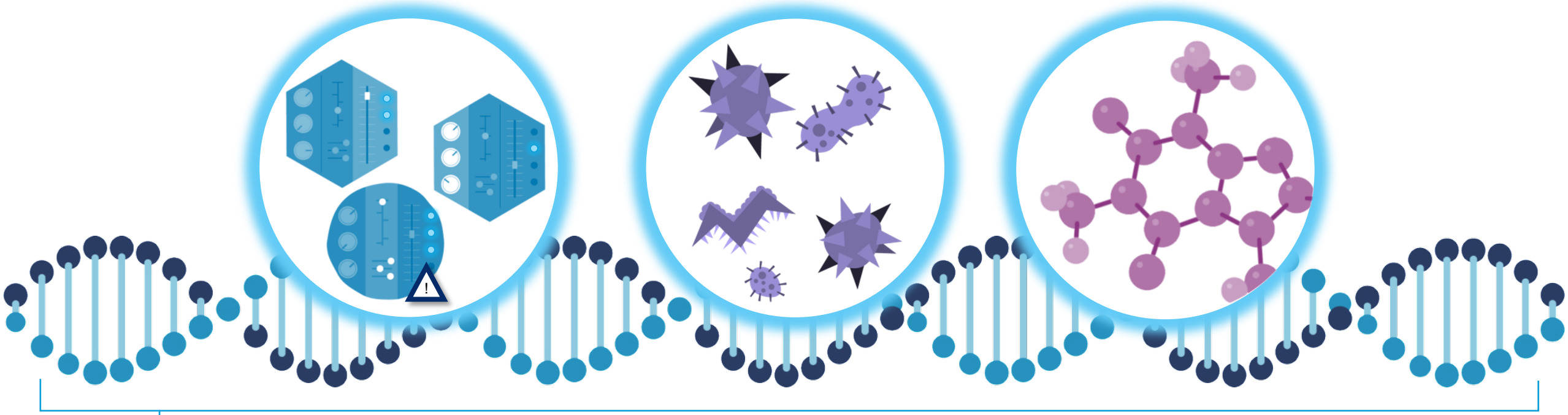
Gene Control Discovery Engine

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

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Robust early-stage pipeline to fuel long-term growth

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

Multiple expected value-driving milestones and strong cash position

Tamibarotene w/ aza	Initiate SELECT-MDS-1 trial in ND HR-MDS	✓
	Potential NDA filing in ND HR-MDS	**2024**
Tamibarotene w/ ven+aza	Initiate SELECT-AML-1 trial in ND unfit AML	**2H 2021**
	Initial data from SELECT-AML-1 trial in ND unfit AML	**2022**
SY-2101	Initiate dose confirmation study	**2H 2021**
	Confirmatory dose/PK data	**1H 2022**
	Initiate Phase 3 registration trial in ND APL	**2022**
	Potential NDA filing	**2024**
SY-5609	Additional dose-escalation data, including clinical activity	ESMO
	Initiate expansion phase of Phase 1	**2H 2021**
Discovery	Name next development candidate	**2022**

Cash into 2023 through multiple expected value drivers

SYROS

Rapidly advancing toward our vision

Now

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

Next

- Progressing into pivotal studies
- Preparing for product launches
- Platform fueling robust pipeline

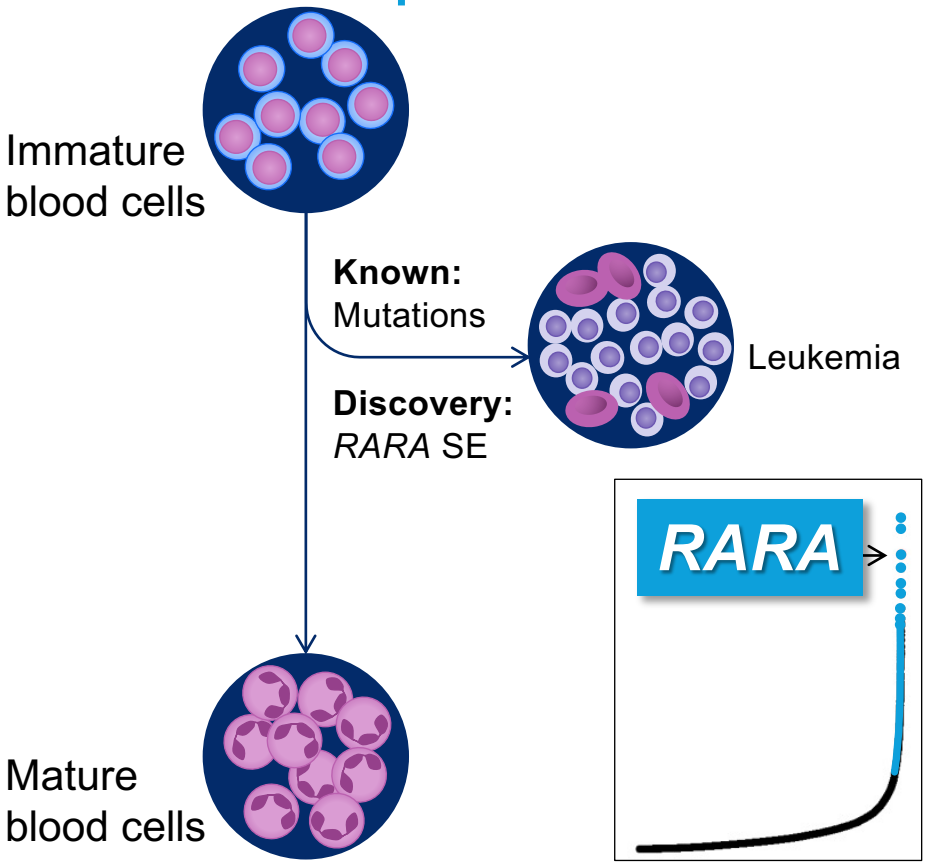
Vision

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

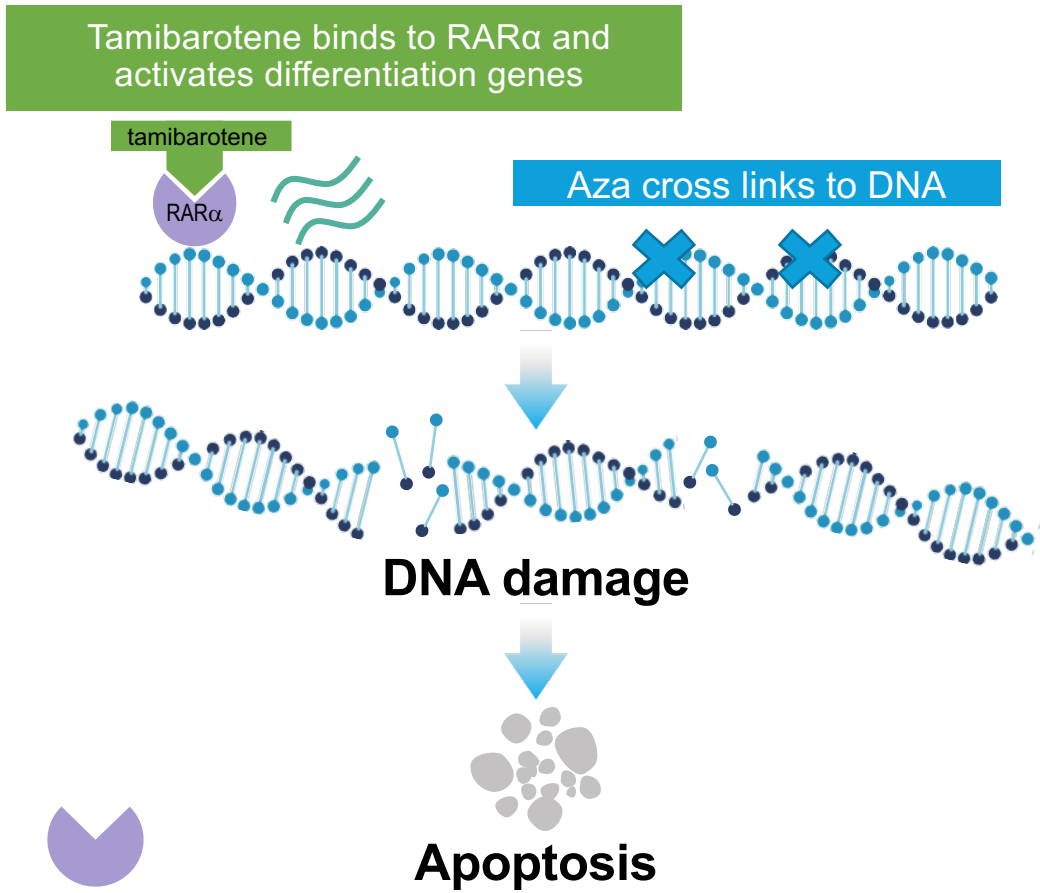
Appendix

Tamibarotene (formerly SY-1425): Novel, first-in-class RARα agonist with broad combination potential

Gene control platform identifies novel patient subset



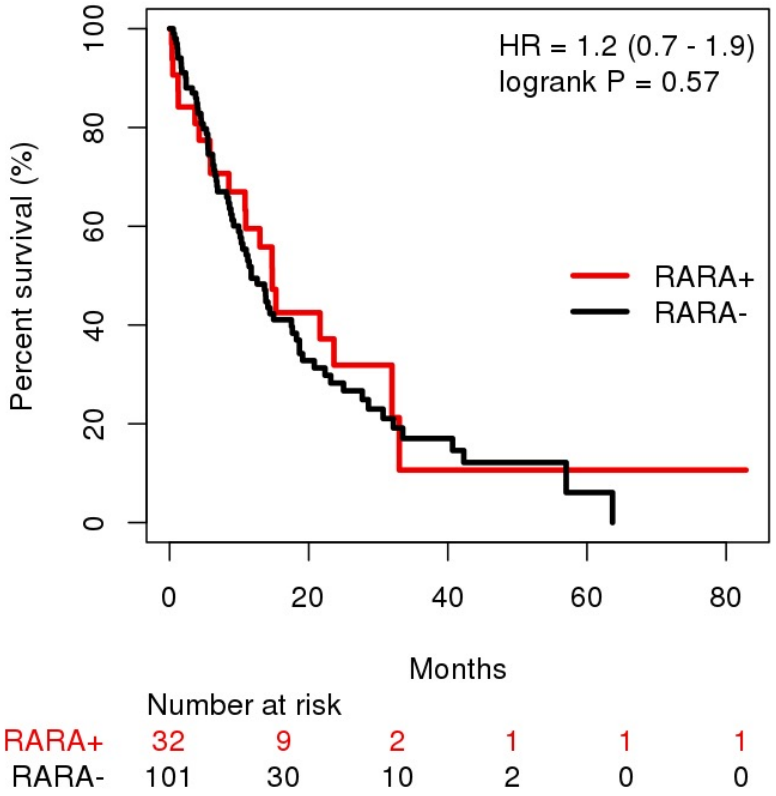
Tamibarotene enhances apoptosis preclinically



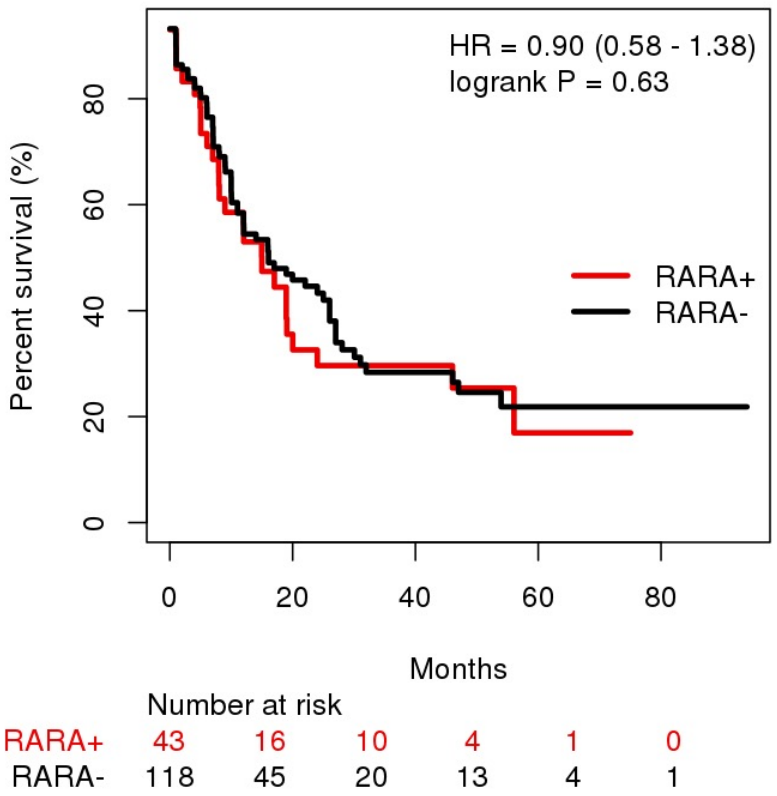
Distinct MOA, tolerability and preclinical synergy with multiple AML agents

RARA is not a prognostic biomarker in AML patients

Analysis of BeatAML Registry RARA expression and survival[1]



Analysis of TCGA RARA expression and survival[2]



- 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 RARa Dependency Targetable by SY-1425, a Potent and Selective RARa Agonist, Cancer Discovery 2017

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Tamibarotene (formerly SY-1425)/azacitidine combination: Clinical activity observed in heavily pretreated RARA-positive R/R AML

- ORR of 19% (4/21) with 2 responding patients continuing on treatment at months 8 and 9, respectively
  - 1 CRc
  - 2 CRi
  - 1 MLFS
- Higher ORR of 43% (3/7) in HMA and ven naïve patients
- Transfusion independence in 30% (6/20)
- Median OS of 5.9 months (95% CI: 3.1, 9.9)

Data presented at ASH 2020 meeting

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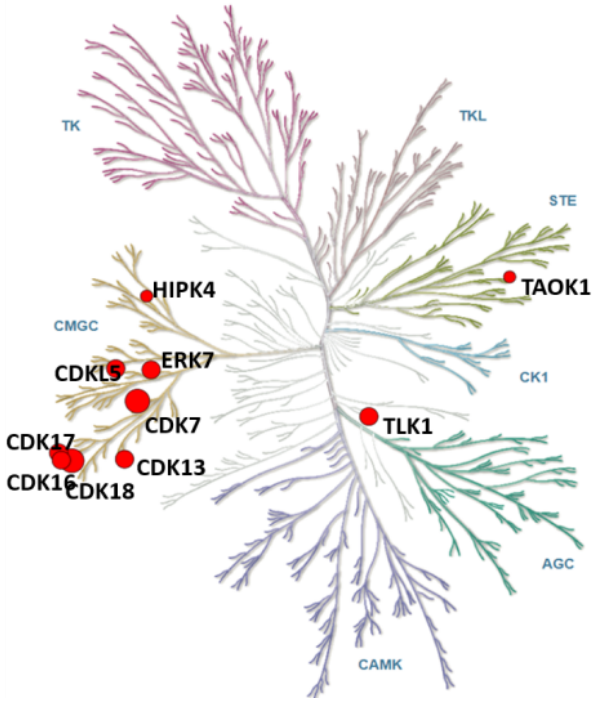
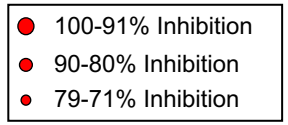
SY-5609: Highly selective and potent oral CDK7 inhibitor



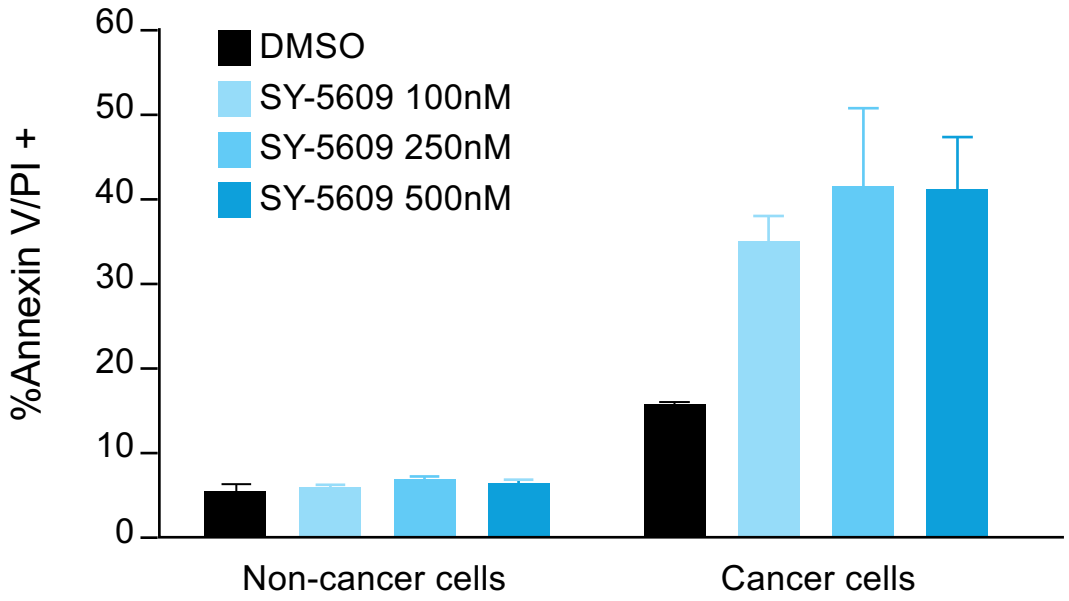


0.06 nM potency for CDK7

13,000- to 49,000-fold more selective for CDK7 over CDK2, CDK9 and CDK12

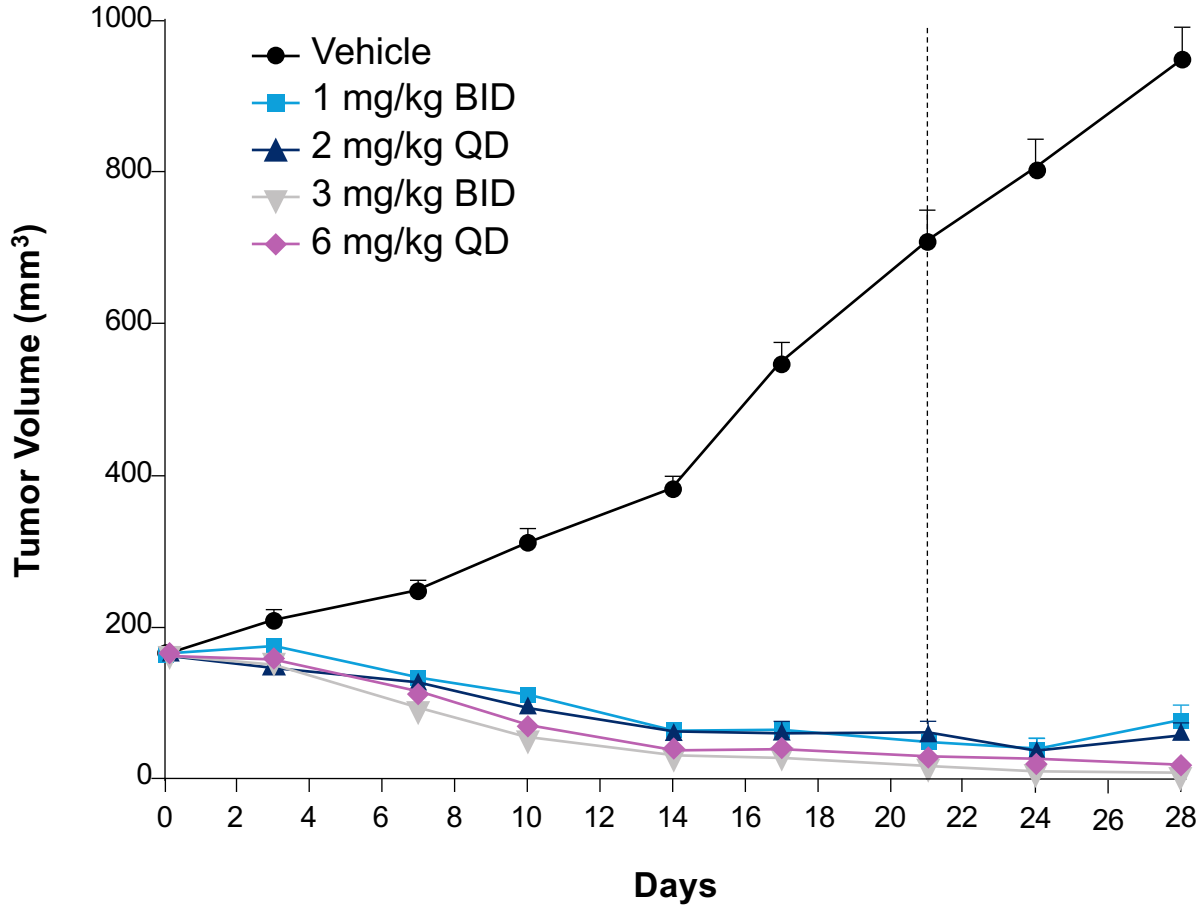
Only 4 of 485 kinases inhibited at ≥ 90%

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



SY-5609: Tumor growth inhibition observed below MTD in preclinical models

Triple negative breast cancer model



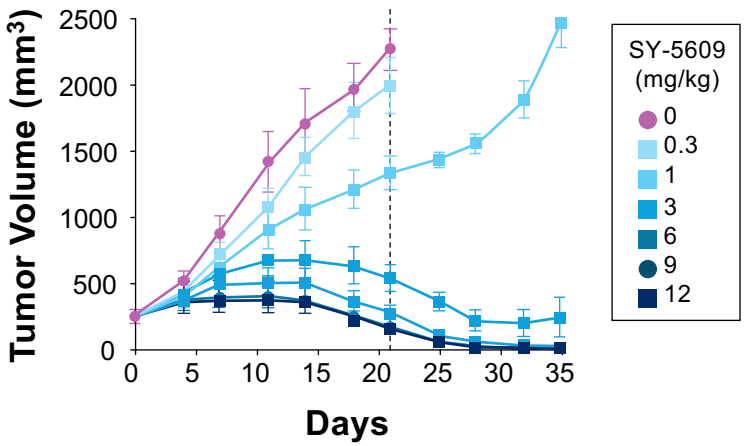
- Regressions observed at 5-fold below MTD of ≥10 mg/kg QD

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

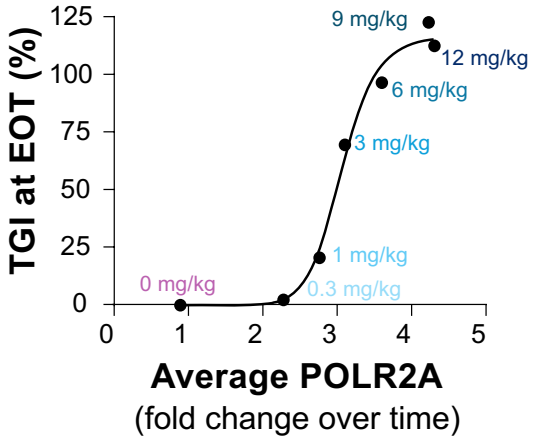
Data presented in October 2019 at EORTC-NCI-AACR Conference

SY-5609: Dose-dependent tumor growth inhibition and PD effects in tumor tissue in preclinical colorectal cancer models

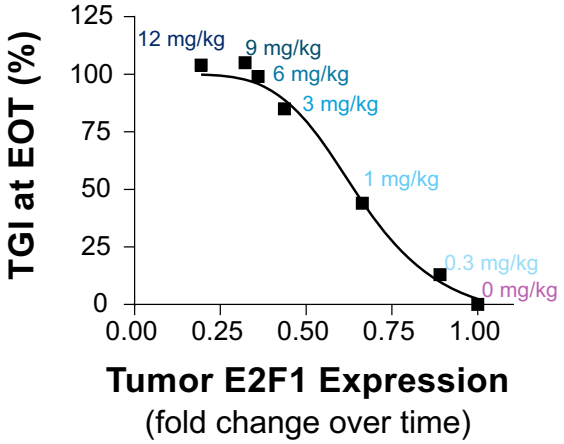
Tumor growth inhibition



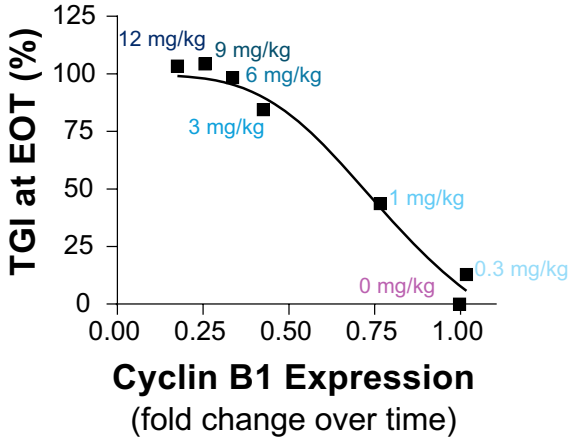
Dose-dependent increase in POLR2A



Dose-dependent decrease in E2F1



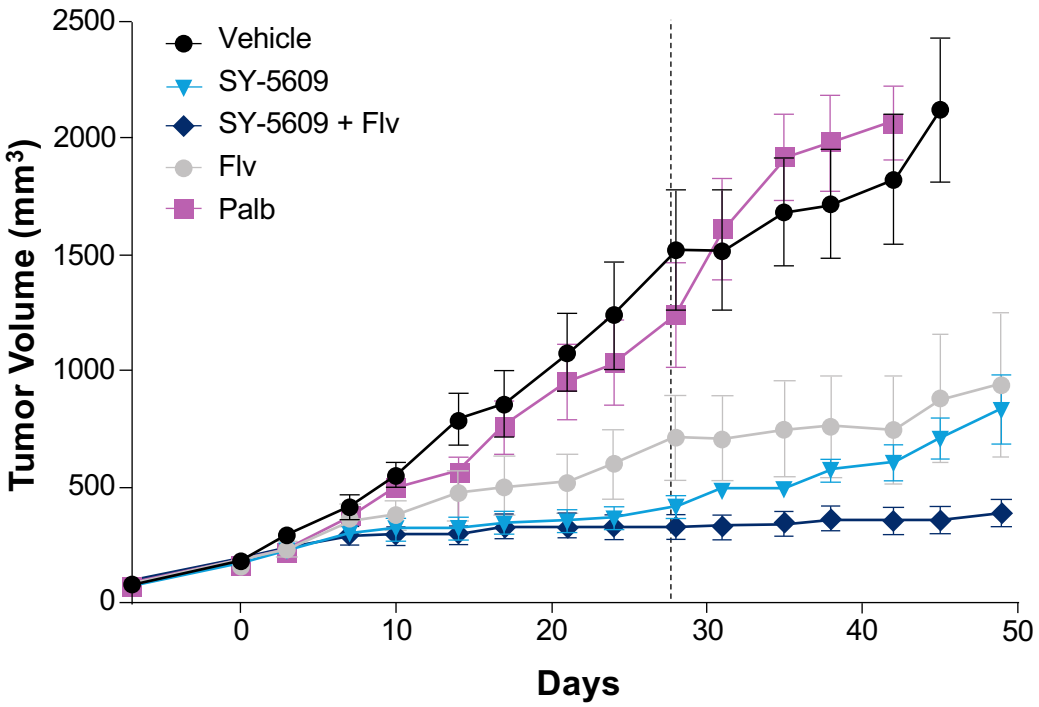
Dose-dependent decrease in cyclin B1



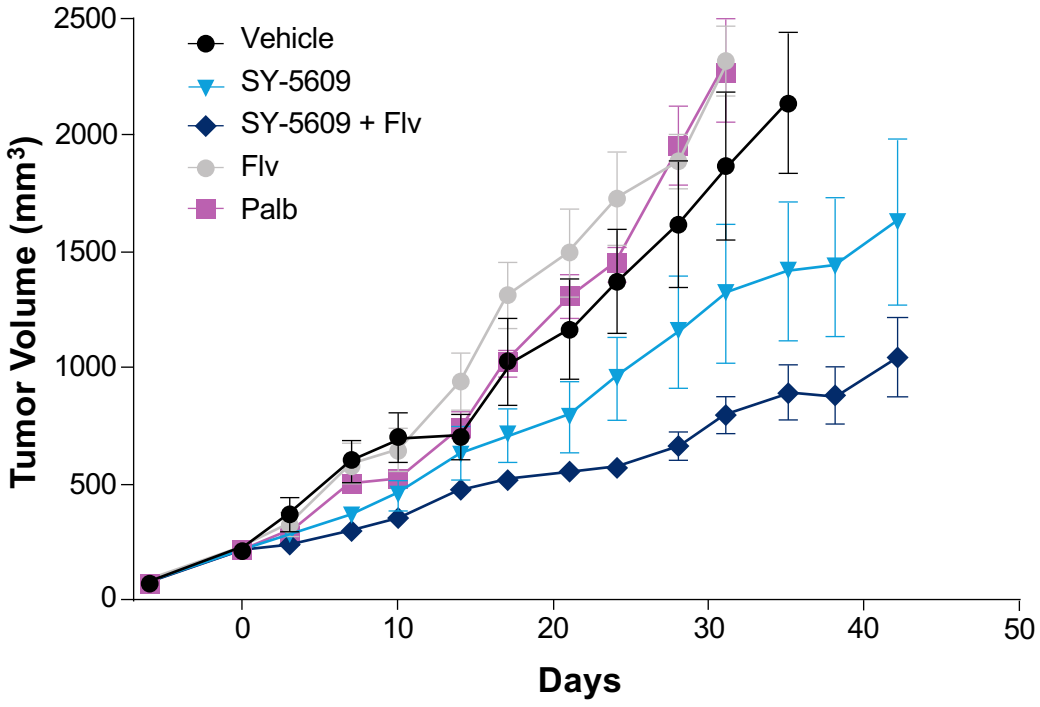
Data presented in May 2020 at ASCO Virtual Symposium

Overcoming treatment resistance: SY-5609 induces robust responses in preclinical HR+ breast cancer models

CDK4/6 inhibitor resistant model



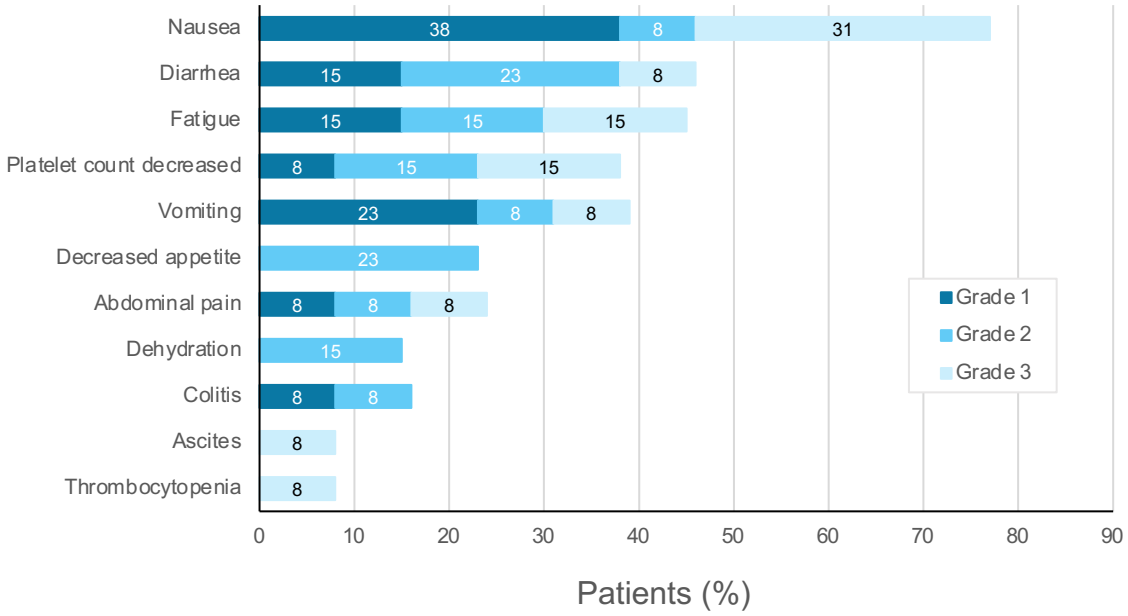
CDK4/6 inhibitor and hormonal resistant model



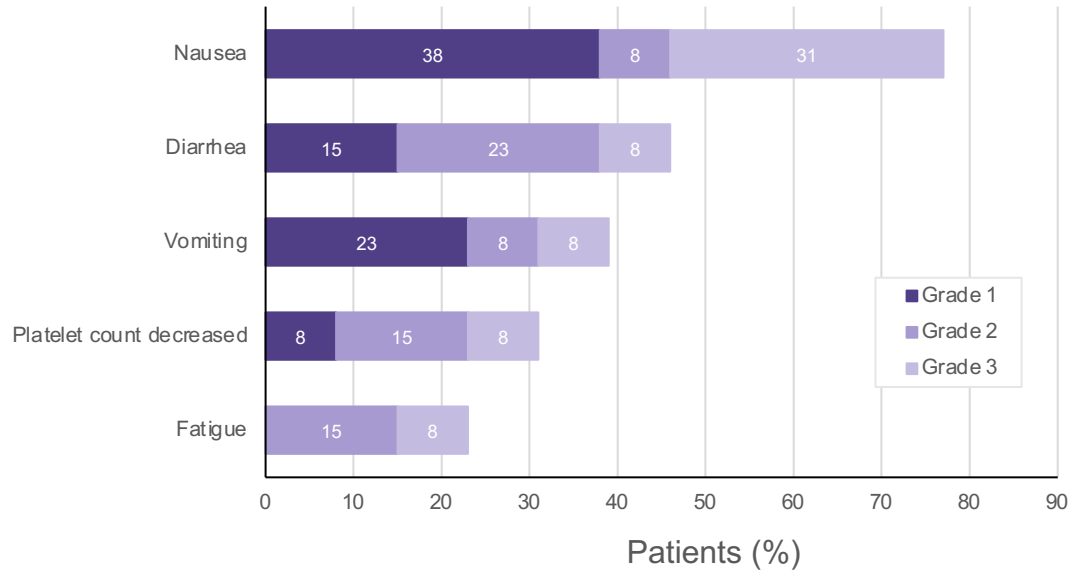
Palb: palbociclib, 50mg/kg once daily, oral; **Flv**: fulvestrant, 2.5mg/kg once weekly, sub-cutaneuous, **SY-5609**: 6 mg/kg once daily, oral

SY-5609: Safety overview from early dose-escalation data (n=17)

Single Agent Adverse Events; All Causality



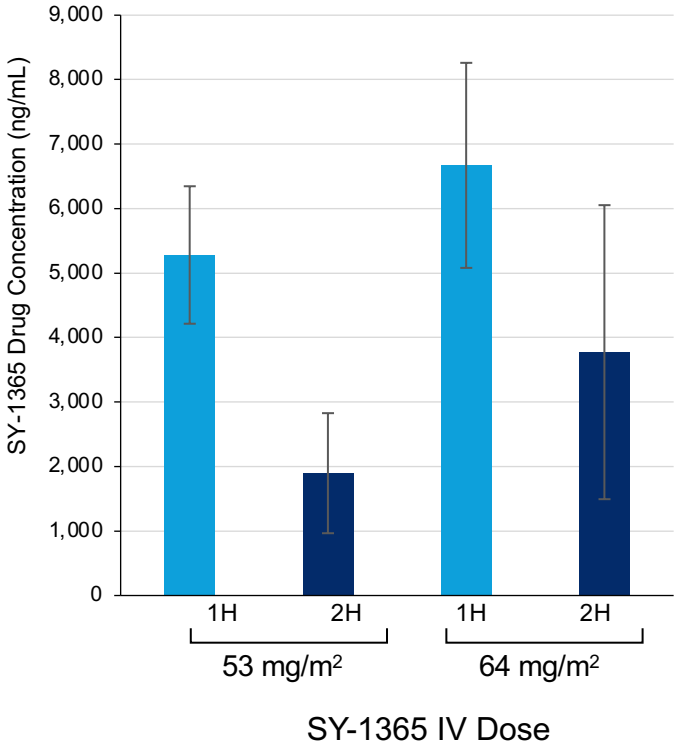
Single Agent Related Adverse Events



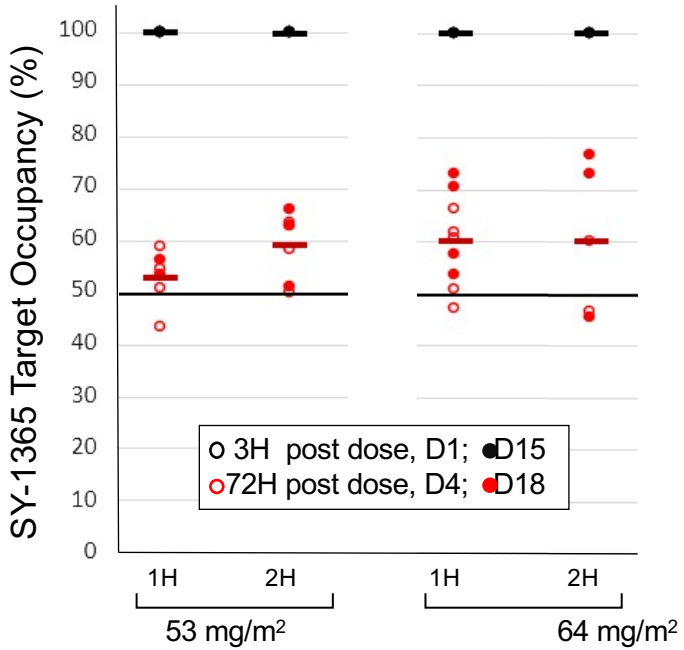
- Predominantly low grade; most frequent related AEs include nausea, diarrhea, fatigue, platelet count decrease and vomiting
- DLTs: nausea and thrombocytopenia (5 mg); fatigue and abdominal pain (4 mg)
- MTD for continuous daily dosing defined as 3 mg
- In patients treated in combination with fulvestrant, safety profile was consistent with single-agent treatment with SY-5609

SY-1365: Peri-infusional AEs in Phase 1 trial were associated with peak blood 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)

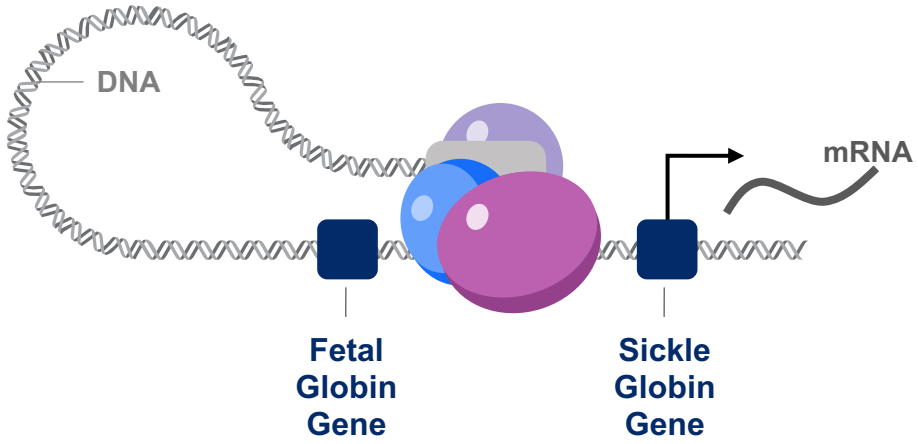
*Includes AEs experienced in patients treated with 53 mg/m² and 64 mg/m²

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

Applying our platform to monogenic diseases: sickle cell disease and beta thalassemia

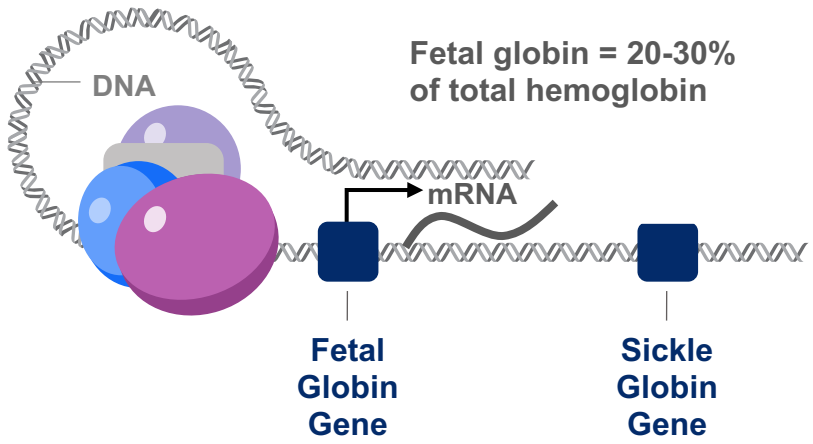
Clinical and genetic data point to therapeutic benefit of elevated fetal globin

- 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



SY-2101 transaction overview and $90.5 million strategic financing

Asset acquisition

- Upfront cash payment of $12 million
- Additional regulatory milestone of $6 million in APL indication
- Aggregate sales milestones of up to $10 million

Strategic financing

- Completed strategic financing yielding $90.5 million in gross proceeds
- Led by Bain Capital Life Sciences with participation from additional new and existing investors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