SY-1365 Phase 1 Dose Escalation

EORTC-NCI-AACR Meeting
November 15, 2018

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

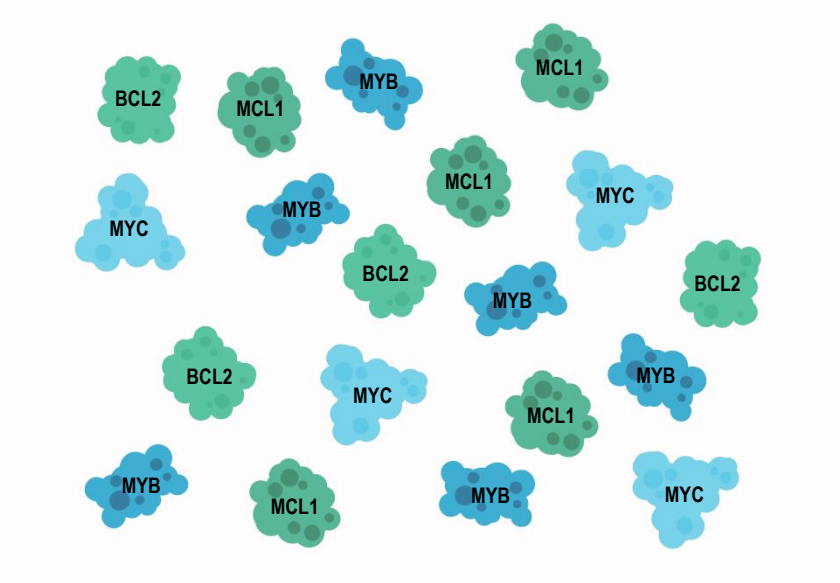
Difficult-to-treat solid tumors and blood cancers

- First-in-class selective inhibitor of CDK7
- CDK7 inhibition induces apoptosis and preferentially kills cancer cells over non-cancerous cells
- Currently in Phase 1 clinical trial as single and combination agent in ovarian and breast cancers
  - Opened expansion cohorts in September 2018
  - Data from dose escalation phase presented today in oral presentation at EORTC-NCI-AACR 2018 meeting
- Broad potential to expand into additional solid tumors and blood cancers

CDK7 has emerged as a potentially important target across a range of solid tumors and blood cancers

Transcription

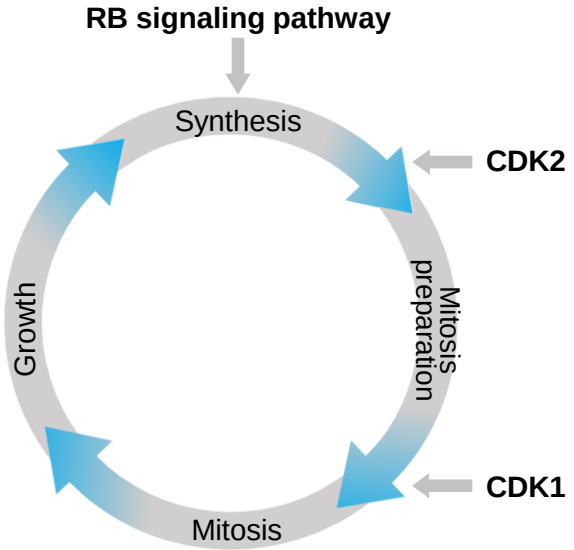
Certain cancers hijack transcriptional machinery to drive increased expression of oncogenic transcription factors and anti-apoptotic proteins



CDK7

Cell Cycle

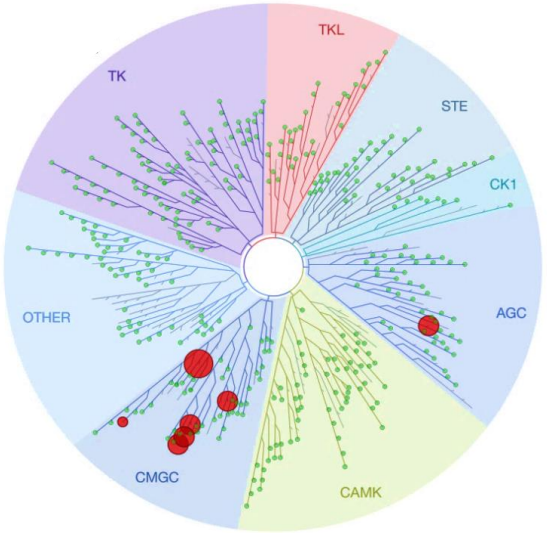
Certain cancers develop adaptations to progress through the cell cycle despite damaged DNA and genomes



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

- Covalent
- Highly potent
- Highly selective
  - Only binds to 7 out of 468 kinases screened at >90% binding
  - Does not significantly bind to CDK9 or cell cycle CDKs
- Preclinical models demonstrated sustained CDK7 occupancy levels >50% maximized antitumor effects, and supported intermittent dosing
- Durable tumor responses in *in vivo* models

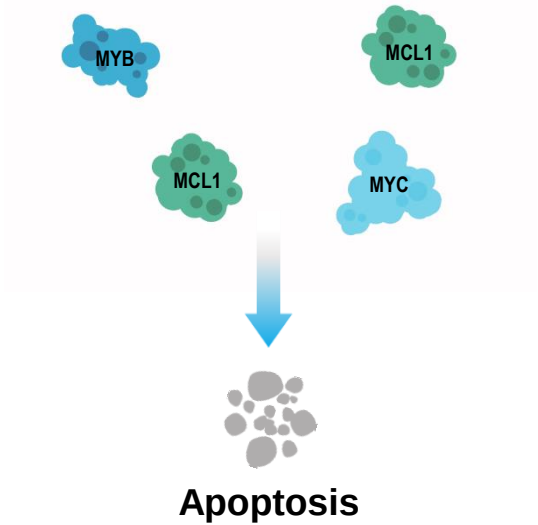
DiscoveRx kinome scan at 1μM SY-1365



SY-1365 has dual effect on transcription and cell cycle, preferentially killing cancer cells in preclinical studies

Transcription

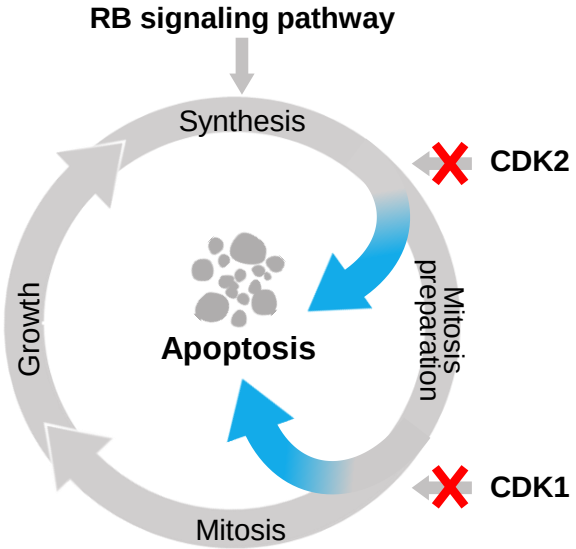
SY-1365 has been shown to decrease expression of oncogenic transcription factors and anti-apoptotic proteins in multiple preclinical models



SY-1365

Cell Cycle

SY-1365 is thought to interfere with these adaptations at multiple points in the cell cycle, promoting the induction of apoptosis



Expansion cohorts in Phase 1 trial exploring SY-1365 as single agent and in combination in multiple ovarian and breast cancer patient populations

Phase 1 clinical trial design

Dose escalation

Status: Completed, data at EORTC-NCI-AACR

- Enrolled patients with advanced solid tumors of any histology
- Explored once- and twice-a-week dosing
- Primary objective to establish MTD and optimal dose and regimen
- Assessed safety, PK/PD, proof-of-mechanism

Expansion

Status: Ongoing

Relapsed ovarian cancer, 3+ prior lines
Single agent (N=24)

Relapsed ovarian cancer, 1+ prior lines (platinum sensitive)
Combination with carboplatin (N=24)

Primary platinum refractory ovarian cancer
Single agent pilot (N=12)

HR+ metastatic breast cancer, CDK4/6 inhibitor resistant
Combination with fulvestrant (N=12)

Solid tumors accessible for biopsy
Single agent (N=10)

Dose escalation portion of SY-1365 Phase 1 trial

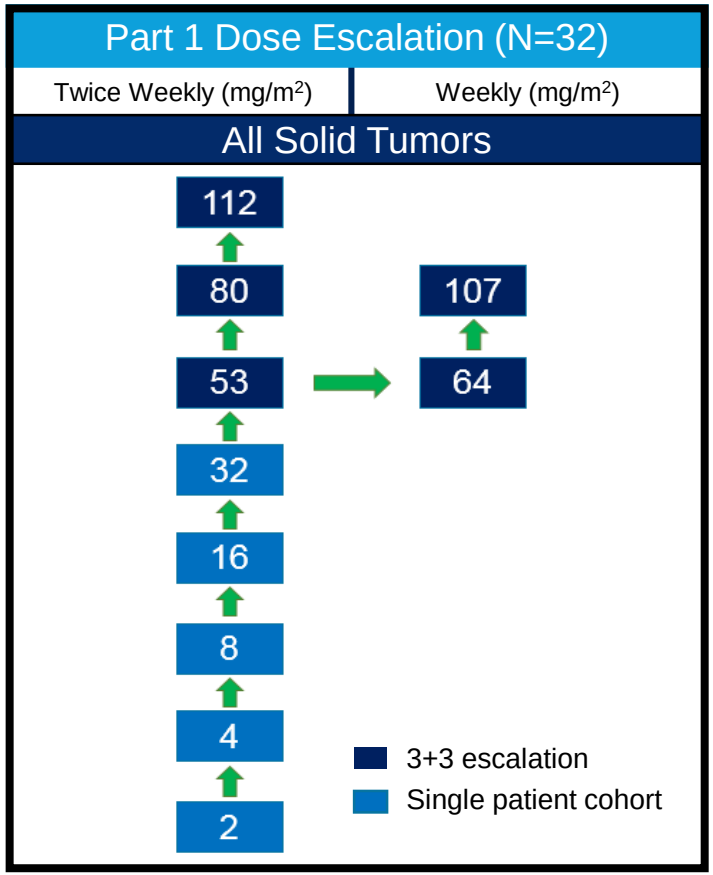
Dosing

- IV dosing over one hour
  - 3 weeks every 4 weeks

Trial Endpoints

- **Primary:** DLTs and safety
- **Secondary:** PK and PD
- **Exploratory:** Anti-tumor activity

Data snapshot: Oct. 15, 2018



SY-1365 dose escalation: patient baseline characteristics

Characteristics N(%)	N=32
Median Age, years (range)	63 (25-87)
Female sex, n (%)	25 (78.1)
≥4 Prior Lines of Therapy	28 (87.5)
Median Number Prior Lines (range)	5 (1-13)
Cancer Type	
Breast	8 (25)
Ovarian	8 (25)
Endometrial	5 (16)
Pancreatic	2 (6)
Other	9 (28)

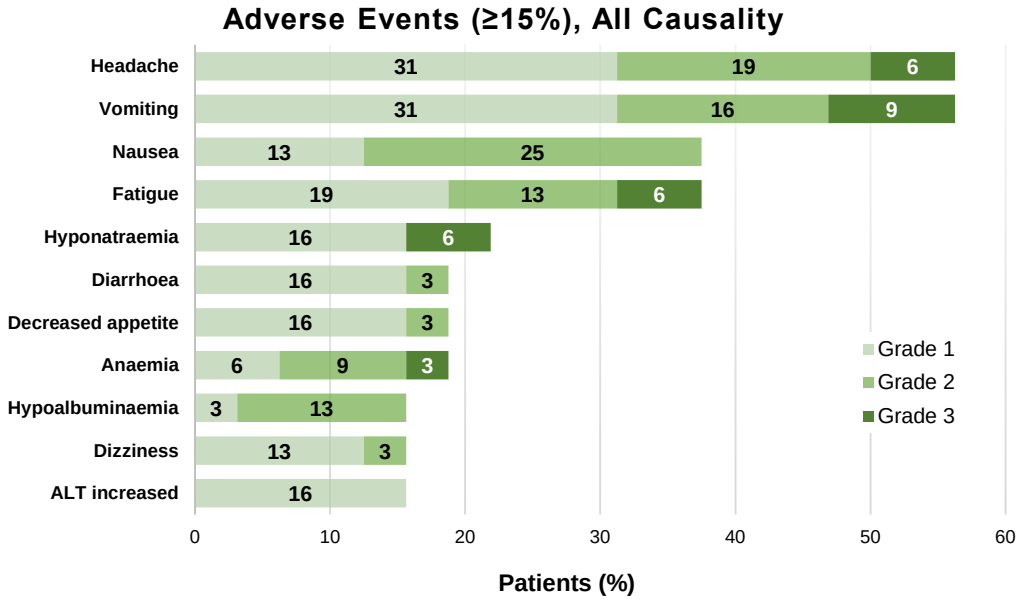
SY-1365 dose escalation: patient disposition

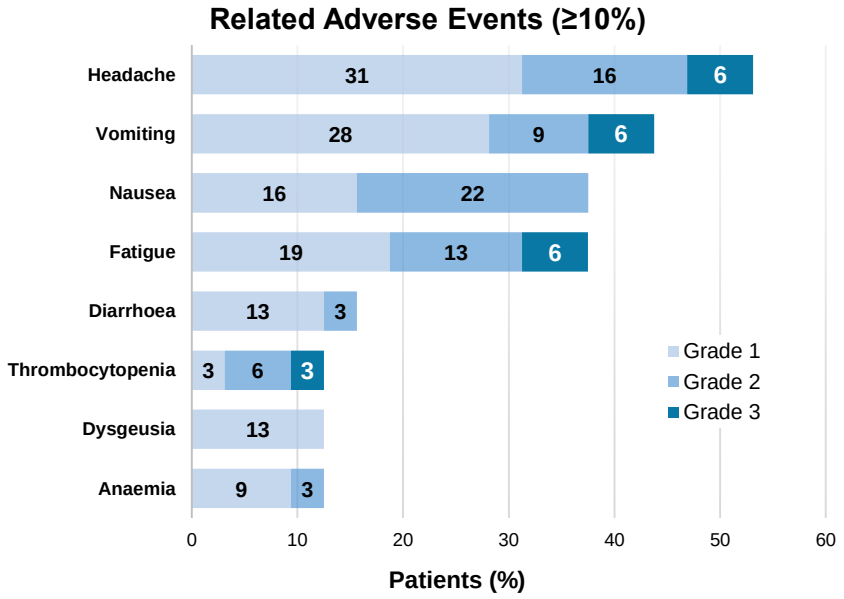
Number of Patients Enrolled By Dose Level											N
Dose (mg/m^2)	**2**	**4**	**8**	**16**	**32**	**53**	**64**	**80**	**107**	**112**	**Total**
Safety Population	1	2	1	1	1	6	7	6	6	1	**32**
Response Evaluable	1	1	1	1	1	3	5	3	3	0	**19**

Number of Patients Enrolled	N (%)
Duration of Treatment: Median days (range)	**46.5 (2 – 147)**
Patients withdrawn from treatment	**28 (87.5)**
Progressive Disease per RECIST 1.1	16 (50.0)
Clinical Progression	7 (21.9)
Withdrawal of Consent	4 (12.5)
Death*	1 (3.1)

*Due to progression of disease

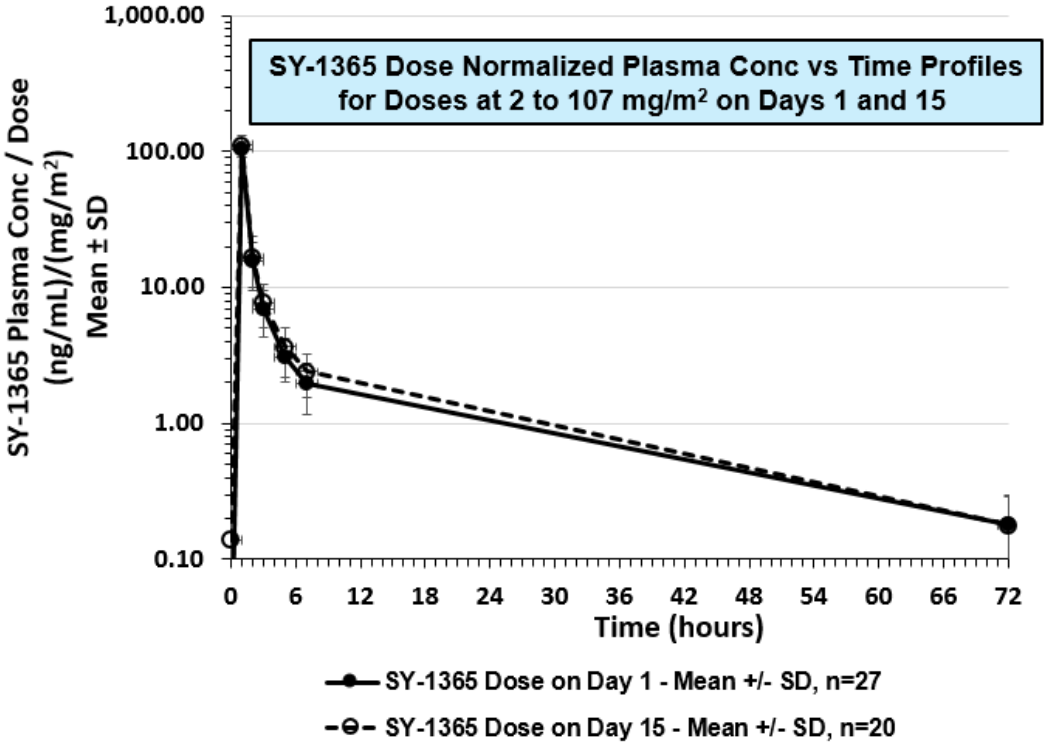
SY-1365 safety overview: dose escalation (N=32)





- Predominantly low grade, reversible, and generally manageable
- Most frequent related AEs include headache, nausea, vomiting, and fatigue
- No reports of neutropenia
- DLTs: headache (64 mg/m^2), coronary vasospasm (80 mg/m^2), and fatigue (112 mg/m^2)
- MTD not defined

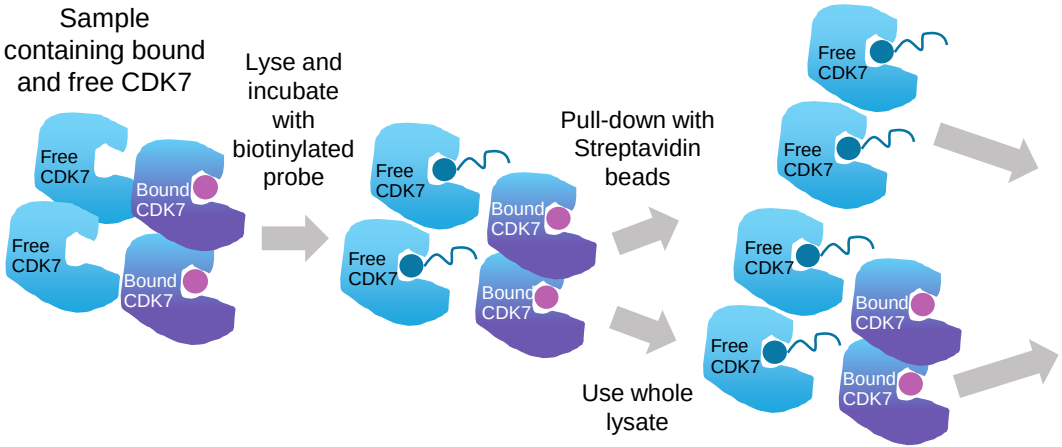
SY-1365 plasma pharmacokinetics



- Plasma PK exposures (Cmax, AUC) are linear from doses of 2 to 107 mg/m^2
- No SY-1365 accumulation with repeat dosing
- SY-1365 day 1 PK parameters at 80 mg/m^2
  - Cmax: 7,498 ± 1,116 ng/mL
  - AUC: 11,696 ± 2,848 ng/mL•h
  - Half-life: 17.9 ± 4.2 h

SY-1365 PD effects evaluated by CDK7 occupancy and transcriptional assays

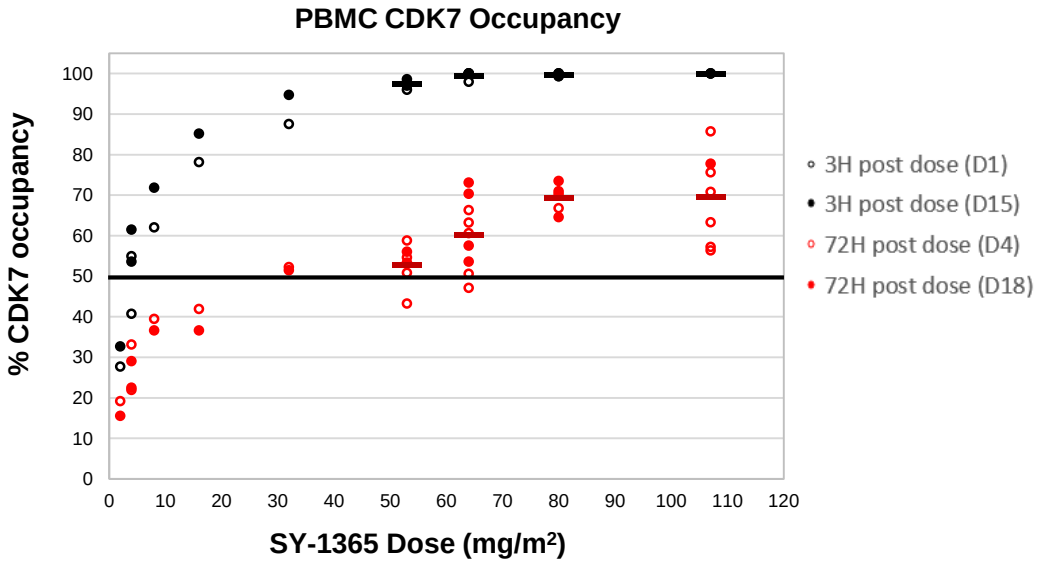
- CDK7 Occupancy: relative measure of free CDK7 to total CDK7

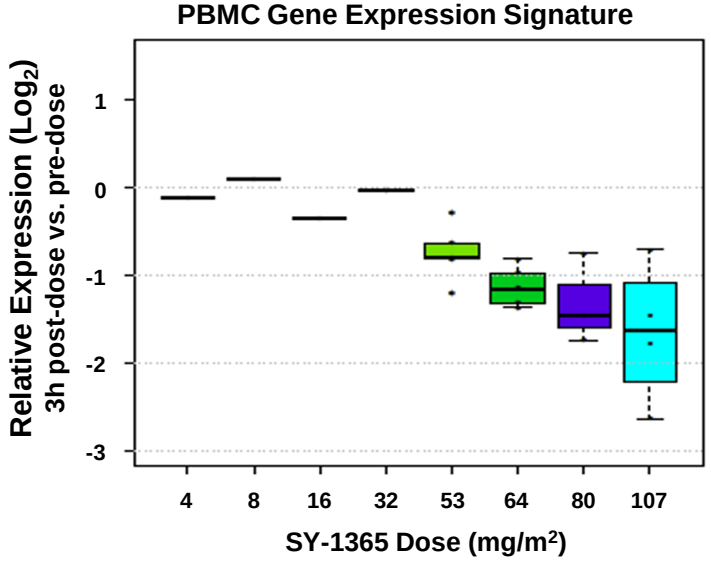


- SY-1365-biotin probe molecule to capture unbound/free CDK7
- MSD format for high-throughput assessment

- Transcriptional assay: gene expression signature
  - SY-1365 dose-response gene signature developed in PBMCs *in vitro*
  - ~25 early response genes (3-5 hrs post treatment)
  - Custom Nanostring codeset to evaluate a subset of response and control genes in patient PBMCs

SY-1365 demonstrates dose-dependent effects on CDK7 occupancy and gene transcription





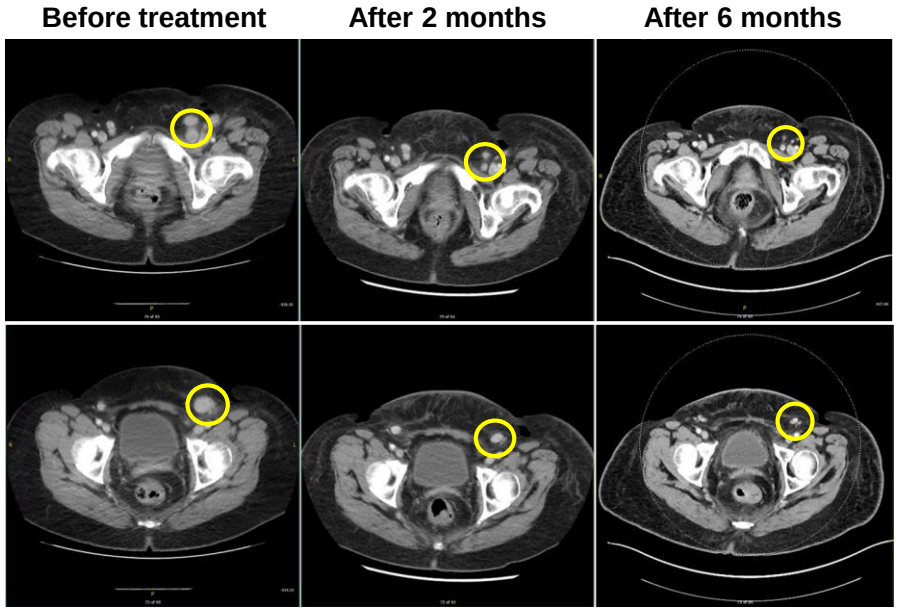
- SY-1365 binding to CDK7 over the dosing interval exceeded target levels from preclinical efficacy models at doses ≥ 32 mg/m^2 with plateauing at 80 mg/m^2 and above
- Similar %CDK7 occupancies observed between PBMCs and xenograft tissues in syngeneic mouse studies, and between PBMCs and tumor biopsies collected from patients (n=2)
- Transcriptional assay demonstrated SY-1365 dose response relationship with gene expression changes

Early evidence of SY-1365 clinical activity

- Clinical activity per RECIST 1.1 criteria was observed in 7 out of 19 evaluable patients
  - Disease Control Rate (CR+PR+SD) of 37%
- One confirmed PR (in clear cell ovarian cancer patient) observed at 80 mg/m^2 BIW
- 6 additional patients with stable disease, mostly at higher doses (≥ 32 mg/m^2 BIW)
  - Consists of 2 ovarian, 2 breast and 2 endometrial cancer patients
  - Duration of treatment for these patients ranged from 50 - 127 days

Early evidence of SY-1365 clinical activity

- CT images of 52 year old woman with relapsed ovarian cancer on SY-1365 80 mg/m2 BIW



- Stage IV clear cell in 4th relapse
  - ARID1A, PIK3CA, NF1 mutations
- Best response to prior lines of therapy: SD
- Confirmed PR after 2 cycles
  - 31.8% reduction (C3D1)
- Remains on study in PR in 7th month of SY-1365 treatment
  - 49% decrease at C7D1

Dose and schedule selected for ongoing expansion cohorts

- Evaluating SY-1365 as single agent and in combination in multiple ovarian and breast cancer patient populations
- Dose selection supported by PK/PD analyses of drug exposure and target occupancy, tolerability profile and early signs of clinical activity
  - Single agent: 80 mg/m^2 twice weekly
  - Combination: 80 mg/m^2 once weekly

SY-1365 Phase 1 Expansion Cohorts

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Single agent (N=24)

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Significant need for new therapies in advanced high-grade serous ovarian and HR+ metastatic breast cancer

Ovarian Cancer : ~59,000[1]

- 70% have high-grade serous ovarian cancer and most present with advanced disease at initial diagnosis
- Standard-of-care includes platinum-based chemotherapy as foundation
  - Majority of patients, even those who initially respond to platinum-based chemotherapy, relapse within a year
- Significant unmet need and/or limited treatment options in platinum sensitive, resistant and refractory patients

Breast Cancer : ~266,000[2]

- ~80% are HR+ breast cancer
- Standard-of-care for metastatic HR+ breast cancer includes CDK4/6 inhibitor plus an aromatase inhibitor
  - ~50% of patients progress within ~2 years
- Second-line hormone-based therapies have limited efficacy, creating a need for new therapies

[1]Annual ovarian cancer diagnoses in the U.S., Canada, Japan and the EU 5 (UK, Germany, France, Spain and Italy). Health Advances analysis.

[2]American Cancer Society estimate of new cases diagnosed in U.S. in 2018

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

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Future

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
- Ongoing investment in discovery

Now

- Driving SY-1425 and SY-1365 to key milestones
- Advancing SY-5609 into IND-enabling studies
- Investing in discovery to support goal of one IND every other year
- Cash to fund planned operations into 2020


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