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Early Evidence of Dose-dependent Pharmacodynamic Activity Following Treatment with SY-5609, a Highly Selective and Potent Oral CDK7 Inhibitor, in Patients with Advanced Solid Tumors

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Abstract # 180

Early Evidence of Dose-dependent Pharmacodynamic Activity Following Treatment with SY-5609, a Highly Selective and Potent Oral CDK7 Inhibitor, in Patients with Advanced Solid Tumors

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Background

- CDK7 controls two key processes which when deregulated, are important in the development of cancer: transcription and cell cycle control
- SY-5609 is an oral, noncovalent, highly selective and potent CDK7 inhibitor:
  - Demonstrates robust anti-tumor activity at well-tolerated doses in patient-derived xenograft (PDX) models with enrichment for deep and durable responses in models with oncogenic alterations in the RB pathway (SCLC, TNBC, HGSOC) and MAPK-pathway (CRC, PDAC, NSCLC)
  - Demonstrates robust anti-tumor activity in combination with fulvestrant at well-tolerated doses in HR+BC PDX models resistant to CDK4/6 inhibitor treatment
- Preclinical *in vivo* studies identified a PD gene expression marker, POLR2A mRNA, associated with SY-5609 dose-dependent tumor growth inhibition (Johannessen, ASCO 2020, Poster #3585)
- Preclinical data support tumor growth inhibition in preclinical models when SY-5609 is dosed with a continuous or intermittent dosing regimen
- A phase 1 first in human dose escalation study (NCT04247126) was initiated to evaluate the optimal dose and regimen as a single agent in select solid tumors, and in combination with fulvestrant in hormone receptor positive breast cancer (HR+BCA)*
- Here we report initial results with a focus on safety, tolerability, PK, and PD (POLR2A) in the 28-day single agent continuous daily dosing regimen and the 3 week on, 1 week off fulvestrant combination regimen

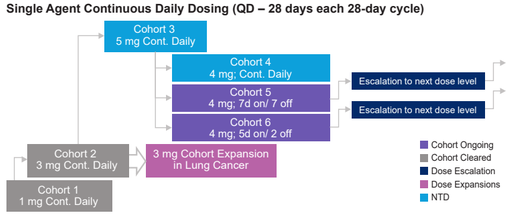
* Papadopoulos, ASCO 2020, Poster #TPS3662

Methods

- Patients were eligible with a diagnosis of advanced breast, colorectal, lung, ovarian or pancreatic cancer or with advanced cancer of any histology with evidence of deregulated RB cell cycle control
- Safety and tolerability, including cycle-1 dose-limiting toxicities (DLTs) were evaluated
- Dose-limiting toxicities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0
- Serial plasma PK, and PD in PBMCs were obtained on days 1 and 15 in cycle 1
- POLR2A mRNA expression within treated patients' PBMCs were measured relative to a set of control genes identified as unresponsive to SY-5609 in preclinical models; POLR2A mRNA fold-change within a patient was determined by normalizing to the pre-dose sample on day 1
- Tumor responses were assessed per RECIST version 1.1
- Data presented from August 21, 2020 snapshot

SY-5609-101 Study Status Summary

Single Agent Continuous Daily Dosing (QD – 28 days each 28-day cycle)



Breast Cancer Combination with Fulvestrant (SY-5609 dosed 3 weeks on; 1 week off)

Single agent

- 3 mg identified as MTD in continuous daily dosing cohort
  - 2 DLTs each at 5 mg and 4 mg dose levels
    - 5 mg: Grade 3 nausea (1) and thrombocytopenia (1)
    - 4 mg: Grade 3 fatigue (1) and abdominal pain (1)
- Alternate regimens ongoing
  - 7 days on / 7 days off; 4 mg
  - 5 days on / 2 days off; 4 mg
- Lung cancer expansion ongoing at 3 mg continuous daily dosing

Combination with fulvestrant

- Enrollment at 3 mg daily was expanded and continues following safety clearance
- Dose escalation of the combination is ongoing

Baseline Characteristics, N (%)	N=17 (100)
Median Age, Years (range)	64 (48-76)
Gender, n (%)	
Female	14 (82)
Male	3 (18)
Median Number of Prior Lines (range)	4 (1-12)
≥ 5 Prior Lines of Therapy, n (%)	8 (47)
Tumor Type, n (%)	
Breast CCND1 amplification, N=1 RB1 deletion, N=1	5 (29)
Colorectal CCND2 amplification, N=2	4 (24)
Ovarian CCNE1 amplification, N=2	4 (24)
Pancreatic CDKN2A mutation, N=2	2 (12)
Endometrial CCNE1 amplification, N=1	1 (6)
Esophageal CCNE1 amplification and CDKN2A deletion, N=1	1 (6)

59% (10/17) of patients enrolled had previously detected mutations indicative of deregulated RB cell cycle control

SY-5609 Patient Disposition

Number of Patients Enrolled by Dose Level

	SY-5609 Single Agent Cohorts				SY-5609 + Fulvestrant Combination Cohort	N
Dose (mg)	**1**	**3**	**4**	**5**	**3**	**Total**
Safety Population[a]	1	4	3	5	4	17
Response Evaluable[b]	1	3	0	1	1	6

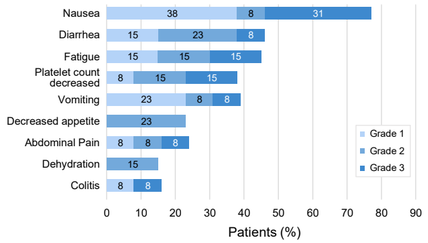
Number of Patients Enrolled, N (%)

	SY-5609 Single Agent Cohorts N=13	SY-5609 + Fulvestrant Combination Cohort N=4
Duration of Treatment: Median Days (range)	**40 (7-156)**	**34 (3-49)**
Patient Withdrawn from Treatment	**6 (46)**	**1 (25)**
Disease Progression[c]	3 (23)	1 (25)
Adverse Event	1 (8)	0 (0)
Withdrew Consent	1 (8)	0 (0)
Other (entered hospice)	1 (8)	0 (0)

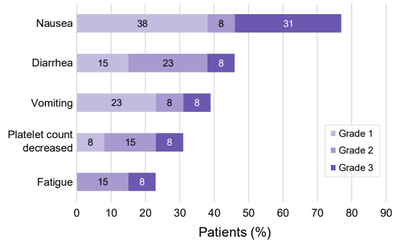
(a) Safety population was defined as patients who took at least one dose of study drug (SY-5609) (b) All enrolled patients who received at least 1 dose of study drug and have at least 1 post-baseline disease assessment
(c) Per RECIST v1.1

SY-5609 Safety Overview

Single Agent Adverse Events (≥15%); All Causality



Single Agent Related Adverse Events (≥15%)



- Single agent SY-5609 Safety Summary
  - The majority of reported AEs were low grade
  - The most common AEs* were nausea, diarrhea, fatigue, platelet count decrease and vomiting
  - 4/13 (31%) patients developed an SAE (all causality): nausea and ascites, fatigue, colitis, vomiting
- In the 4 patients treated with combination SY-5609 and fulvestrant, the safety profile was consistent with that seen for single agent treatment

A subject was counted only once within each preferred term
*Most common AE defined as those observed in ≥ 25% of the patients

Response Summary

6 of 17 patients were response evaluable

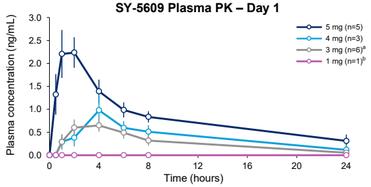
Single Agent Cohort:
- 2 patients at 3 mg daily achieved stable disease as the best response
  - Includes 1 patient with HR+ breast cancer and 1 patient with colorectal cancer
- 1 patient at 5 mg daily achieved stable disease as the best response
  - Patient with esophageal cancer (CCNE1 amplification and CDKN2A deletion)
- 2 patients, 1 each at 1 mg and 3 mg daily demonstrated progressive disease
  - Both patients with ovarian cancer (1 with CCNE1 amplification at 3 mg dose)

Combination Cohort:
- 1 patient demonstrated progressive disease

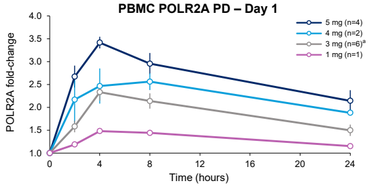
11 of 17 treated patients were not response evaluable at the time of the data-cut
- 2 patients had discontinued treatment prior to the first response assessment timepoint
  - 1 patient at 3 mg and 1 patient at 5 mg
- 9 patients had not reached the first response assessment timepoint at the time of the data-cut
  - 3 patients each at 3 mg, 5 mg and in the combination regimen

Dose-dependent Increases Observed in SY-5609 Plasma Exposures and PBMC POLR2A PD Responses

SY-5609 Plasma PK – Day 1



PBMC POLR2A PD – Day 1



SY-5609 Pharmacokinetic Parameters

Dose (mg)	N*	Day	T_{max} (h) Median (min; max)	C_{max} (ng/mL) Mean (CV%)**	AUC_3 (ng*h/mL) Mean (CV%)**	AUC_{tau} (ng*h/mL) Mean (CV%)**
3	5	1	2 (2, 6)	0.833 (36.1)	3.89 (40.4)	
	4	15	2 (1, 2)	1.22 (29.4)	8.31 (27.7)	20.5 (32.2)
4	3	1	4 (2, 4)	0.916 (58.0)	4.07 (50.4)	
	3	15	4 (2, 4)	1.13 (23.8)	7.62 (24.6)	19.1 (25.9)
5	5	1	1 (1, 2)	3.04 (9.15)	12.4 (12.3)	
	1	15	4	1.46	9.39	NA

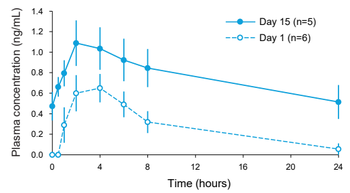
Note: 3 mg group contains data from single agent and combination patients
* Patients with evaluable PK
** Results reported as geometric mean (geometric mean CV%)

- SY-5609 exhibited approximately dose proportional PK with moderate-high interpatient variability and minimal accumulation on repeat dosing
- SY-5609 had a half-life at steady state (~15 hrs) compatible with once daily dosing
- Co-administration with fulvestrant had no impact on PK of SY-5609
- POLR2A PD responses measured on Day 1 across all dose levels had dose-dependent increases over 24 hours

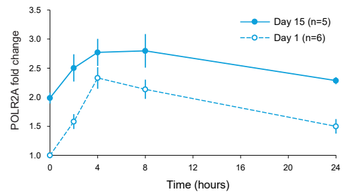
Results for each dose and timepoint represent mean +/- standard error
(a) Includes 2 patients treated in combination with fulvestrant, comparable PK and PD observed between patients treated with 3 mg single agent SY-5609 versus in combination with fulvestrant
(b) Concentrations < BLQ (0.3 ng/mL)

Increased SY-5609 Plasma Exposures and PBMC POLR2A PD Responses Achieved at Steady State with Once Daily Dosing

SY-5609 Plasma PK – 3 mg QD Day 1 vs Day 15



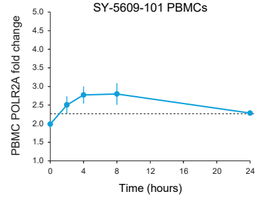
PBMC POLR2A PD – 3 mg QD Day 1 vs Day 15



- PK and PD data were available at the 3 mg continuous daily dose level to support an analysis of POLR2A PD at steady state on Day 15
- POLR2A PD responses at Day 15 were enhanced relative to Day 1, consistent with increased SY-5609 exposure at steady state

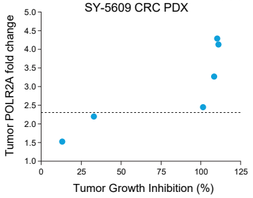
SY-5609 Dosed at 3 mg Daily Induces POLR2A Elevations Associated with Regressions in Preclinical Models and Target Levels of CDK7 Occupancy in Patients

POLR2A PD vs Time
SY-5609-101 PBMCs



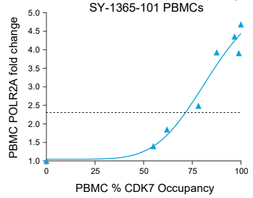
- POLR2A fold-change measured at steady state (day 15)

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 qd, 21d on, 7d off)

POLR2A PD vs CDK7 Occupancy
SY-1365-101 PBMCs

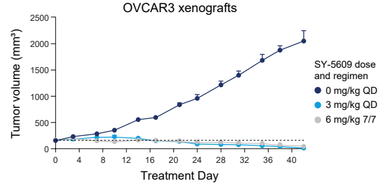


- POLR2A fold-change similar between PBMCs and tumor biopsies

- POLR2A PD responses in PBMCs of SY-5609-101 patients treated at 3 mg attain a ≥ 2.3-fold change from baseline that is consistent with:
  - POLR2A responses in tumor tissue at daily doses that induce regressions (>100% TGI) in BRAF-mutant CRC patient-derived xenografts
  - 70% CDK7 occupancy in PBMCs from patients treated with the covalent CDK7 inhibitor SY-1365 (Study SY-1365-101)
    - ~70% trough CDK7 occupancy observed at SY-1365 dose associated with apoptosis and clinical activity (durable PR in a heavily pre-treated ovarian clear cell cancer patient) (Juric, ENA 2018)
    - ~70% trough occupancy in tumor tissue associated with regressions in preclinical xenograft models treated with SY-1365

Administration of an Intermittent Dosing Regimen Maintained Tumor Regressions in Ovarian Cancer Xenografts

Tumor volume vs time
OVCAR3 xenografts



- SY-5609 dosed po daily (QD) or with a 7-day-on/7-day-off (7/7) schedule per 28-day cycle; data through day 42 shown, study ongoing; dashed horizontal line represents average starting tumor volume
- Both dosing regimens were well-tolerated: mean body weight changes on day 42 were +8% for 6 mg/kg 7/7 and +4% for 3 mg/kg QD

Conclusions

- SY-5609, a highly selective and potent oral inhibitor of CDK7, showed dose-dependent effects on POLR2A gene expression demonstrating proof of mechanism in patients with advanced solid tumors
- POLR2A PD response at 3 mg QD reached levels associated with tumor regressions in preclinical models, and with CDK7 target engagement at which clinical activity was observed with a first generation intravenous CDK7 inhibitor
- As a single agent and in combination with fulvestrant, SY-5609 exhibited approximately dose proportional PK, moderate-high interpatient variability, minimal accumulation with repeat dosing, and a steady state half-life compatible with once daily dosing
- The emerging safety profile demonstrates that the most common AEs to date were nausea, diarrhea, fatigue, platelet count decrease and vomiting
- MTD has been defined for the continuous daily dosing schedule at 3 mg
- Expansion cohorts in breast and lung cancer patients have opened using the 3 mg dose to further assess PK, PD, and early clinical activity in more homogenous cancer patient populations
- Alternate clinical dosing regimens being explored are supported by preclinical models where tumor regressions were maintained with intermittent dosing

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