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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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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, HGSO) 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)

Baseline Characteristics, N (%)	N=17 (100)
Median Age, Years (range)	64 (48-76)
Gender, n (%)	
Female	14 (82)
Male	3 (18)
≥ 5 Prior Lines of Therapy, n (%)	8 (47)
Median Number of Prior Lines (range)	4 (1-12)
Tumor Type, n (%)	
Breast	
CCND1 amplification, N=1	5 (29)
RB1 deletion, N=1	
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 Safety Overview

- 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

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

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

- 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 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

- 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