**Background**

SY-5609 is a novel, non-autonomous, highly selective dose and PK CDK7 inhibitor.

- Demonstrates robust anti-tumor activity in well-characterized in vitro and preclinical models with strong dose-response relationships in the PBMC, THP-1, 293FT and MDA-MB-231 cell lines.
- Demonstrates robust anti-tumor activity in combination with a well-characterized in vitro and preclinical model with strong dose-response relationships in the PBMC, THP-1, 293FT and MDA-MB-231 cell lines.
- Safety and tolerability, including cycle-1 dose-limiting toxicities (DLTs) were evaluated.
- 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.

**Methods**

- Patients were eligible with a diagnosis of advanced breast, colorectal, lung, ovarian, or pancreatic cancer.
- 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.
- PBMCs and PDXs were obtained on days 1 and 15 in cycle 1.
- PBMC-RNA expression within treated patient PBMCs were measured relative to a set of control genes identified as unresponsive to SY-5609 in preclinical models. PBMC-RNA fold-change was defined by patient normalization to the geometric mean across controls.
- Tumor responses were assessed per RECIST 1.1.
- Data presented from August 21, 2020 snapshot.

**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.
  - 1 patient at 4 mg daily achieved stable disease as the best response.
  - 1 patient at 5 mg daily achieved stable disease as the best response.
- Combination Cohort:
  - 2 patients, each at 1 mg and 3 mg daily demonstrated progressive disease.
  - 1 patient with cancer with concurrent on-target drug therapy, combination therapy (dose and regimen).

**Dose-related Increases Observed in SY-5609 Plasma Exposures and PBMC POLR2A Responses**

- SY-5609 Plasma PK – Day 1
- PBMC POLR2A – Day 1

**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 Regional and Necrosis in Patients with endometrial cancer**

- POLR2A responses in PBMs of SY-5609-101 patients treated at 3 mg achieved a 2.3 fold-change from baseline that is consistent with POLR2A being a cancer driver in tumors that respond to SY-5609.
- ~70% CD75 occupancy in PBMs from patients treated with the control CDK7 inhibitor SY-1385 (Study SY-5609-101).

**Conclusions**

- POLR2A is a pharmacodynamic PD gene expression marker for SY-5609 and is enriched in tumors with CDK7 and CDK19 occupancy.
- SY-5609 exhibits a dose-dependent effect on POLR2A gene expression and is associated with tumor regressions in preclinical models and in vivo.

**Administrative of an Intermitting Dosing Regimen Maintained Tumor Regressions in Ovarian Cancer Xenografts**

- SY-5609, a highly selective and potent oral inhibitor of CDK7, showed dosedependent effects on PK/PD in preclinical models at once daily dosing.
- Dose-dense regimens have been shown to demonstrate proof of mechanism in patients with advanced solid tumors.
- POLR2A PD responses at 3 mg QD reached levels associated with tumor regressions in preclinical models and in vivo.
- As a single agent and in combination with fulvestrant, SY-5609 exhibited approximately dose proportional PK and moderate-high interpatient variability, minimal accumulation with repeat dosing, and a once daily-12 h half-life compatible with once daily dosing.
- The emerging safety profile demonstrates that the most common AEs are nausea, diarrhea, fatigue, platelet count decrease and vomiting.
- MTD has not been defined for the continuous daily dosing schedule.
- 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 numerous human cancer patient populations.
- Alternative clinical dosing regimens being explored are supported by preclinical models where tumor regressions were maintained with intermittent dosing.