**SY-5609 is a potent and highly selective CDK7 inhibitor**

- SY-5609 is more potent and selective than other oral, non-covalent CDK7 inhibitors in clinical development.
- SY-5609 has high affinity for CDK7 (Kd = 0.029 nM) and inhibits I2AR (IC50 = 2 nM), whereas with a 5% inhibition at only 20 nM of CDK9 (1930 nM), CDK12 (13 964 nM), and CDK13 (133 nM).

**Methods**

- SY-5609 was profiled in the SelectScreen panel of 485 kinases (ThermoFisher). Kinases that showed >70% Inhibition at 1µM were considered as potential targets.

- SY-5609 inhibited CDK2, CDK7, and CDK12 with IC50 values of 2900 nM, 0.06 nM, and 0.5 nM, respectively, indicating its highly selective profile.

**Summary**

- SY-5609 is a potent and highly selective CDK7 inhibitor that shows promising preclinical activity in multiple tumor models.

**Conclusions**

- SY-5609 is an oral, non-covalent, potent and highly selective CDK7 inhibitor.
- Daily oral dosing of SY-5609 induces dose-dependent TGI in ovarian and breast tumors with RB pathway alterations.
- SY-5609 induces regrowth resistance in multiple PDX models of RB+ breast cancer.

**Daily oral administration of SY-5609 is associated with dose-dependent plasma exposures, transcriptional PD change in xenograft tissue, and TGI**

- SY-5609 dose-dependently downregulated the E2F7 transcription factor in OVCAR xenograft tumors.
- SY-5609 plasma Cmax (at 2h) on Day 1 increased with dose, reaching 1.5 times the IC50 at 3 mg/kg QD.
- SY-5609 dose (mg/kg) vs Tumor volume (mm3) at Day 28 and Day 42 for the different treatment regimens.

**Deep and sustained SY-5609 responses in TNBC, HGSOC, and SCLC PDX models are associated with RB pathway alterations**

- SY-5609 was administered at a total daily dose of 6 mg/kg by oral gavage, except for TNBC-1, which received 10 mg/kg daily.
- SY-5609 dose-dependent downregulation of the RB1 pathway was observed in xenograft tumors, with >100% TGI or regression 21 days after treatment discontinuation.

**Deep and sustained SY-5609 responses in HGSOC and SCLC PDX models are associated with RB pathway alterations**

- SY-5609 was administered at a total daily dose of 6 mg/kg by oral gavage, except for TNBC-1, which received 10 mg/kg daily.
- SY-5609 dose-dependent downregulation of the RB1 pathway was observed in xenograft tumors, with >100% TGI or regression 21 days after treatment discontinuation.

**Deep and more sustained responses were associated with RB pathway alterations**

- SY-5609 was administered at a total daily dose of 6 mg/kg by oral gavage, except for TNBC-1, which received 10 mg/kg daily.
- SY-5609 dose-dependent downregulation of the RB1 pathway was observed in xenograft tumors, with >100% TGI or regression 21 days after treatment discontinuation.

**SY-5609 induces robust responses in treatment-resistant ER+ BC PDX models**

- SY-5609 induces robust responses in treatment-resistant ER+ BC PDX models.
- SY-5609 was administered at a total daily dose of 6 mg/kg by oral gavage, except for TNBC-1, which received 10 mg/kg daily.
- SY-5609 dose-dependent downregulation of the RB1 pathway was observed in xenograft tumors, with >100% TGI or regression 21 days after treatment discontinuation.

**Summary**

- CDK7 is a key regulator of transcription and cell cycle progression and has been implicated in multiple tumor types driven by aberrant transcription control (e.g., MYC, ERCC1, εCAT) and/or aberrant cell cycle control (e.g., RB1, CDKN1A, CDKN2A alterations).
- SY-5609 is a potent and selective CDK7 inhibitor that is advancing through IND-enabling studies to support initiation of a planned Phase 1 oncology trial in Q1 of 2020.
- Here we report on the:
  - pharmacology and selectivity of SY-5609 in vitro and in vivo across a range of tumor types.
  - relationship between SY-5609-induced tumor growth inhibition (TGI), pharmacokinetics (PK), and tumor tissue pharmacology (TP) effects in xenograft models of high-grade serous ovarian cancer (HGSOC), triple negative breast cancer (TNBC), and small cell lung cancer (SCLC).
  - activity of SY-5609 in patient-derived xenograft (PDX) models from tumor types with transcriptional-and/or cellular activity alterations including RB1, RB pathway, small cell lung cancer (SCLC), and estrogen receptor positive breast cancer (ER+ BC).
- The results highlight the broad potential for SY-5609 across multiple difficult-to-treat cancers and support the development of SY-5609 in patients with selected solid tumor malignancies.

**Conclusions**

- SY-5609 is an oral, non-covalent, potent and highly selective CDK7 inhibitor.
- Daily oral dosing of SY-5609 induces dose-dependent TGI in ovarian and breast tumors with RB pathway alterations observed at doses as low as 1/10 of MTD.
- SY-5609 plasma exposures are dose proportional and do not accumulate with repeated daily dosing at therapeutic doses in mice (1-4 mg/kg).
- SY-5609 induces rapid (4 hours) and sustained (24 hours) dose-dependent transcriptional PD responses in xenograft tumor tissue that correlated with TGI, supporting a QD dosing regimen.
- SY-5609 induces regressions, which are sustained after treatment discontinuation, at well-tolerated doses in multiple PDX models from SCLC, TNBC, and HGSOC; sustained regressions are associated with RB pathway alterations.
- SY-5609 induces robust anti-tumor activity in combination with fulvestrant in treatment-resistant PDX models of ER+ BC breast cancer.
- These results highlight the broad potential for SY-5609 across a variety of solid tumor types.
- A Phase 1 trial of SY-5609 is planned to initiate in Q1 of 2020, with inclusion of breast, ovarian, and lung cancer patients, and patients with solid tumors with RB pathway alterations irrespective of tumor type.