Abstract 2352

SY-5609, a Highly Potent and Selective Oral CDK7 inhibitor, Exhibits Robust Antitumor Activity in Preclinical Models of KRAS Mutant Cancers as a Single Agent and in Combination with Chemotherapy

Presentation 13P

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Introduction

- CDK7 inhibition has been shown to target two fundamental processes in cancer: transcription and cell cycle control
- SY-5609 is a potent, selective, and oral CDK7 inhibitor in development in patients with advanced solid tumors (NCT04247126)
- As previously reported (ASCO 2020), SY-5609 activity in patient-derived xenograft (PDX) models of colorectal cancer (CRC) was associated with oncogenic mutations in BRAF and KRAS, potent stimulators of mitogenic MAPK signaling and downstream transcriptional programs for cell proliferation
- Since oncogenic KRAS mutations are prevalent in pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC) tumors, we evaluated SY-5609 preclinical activity as a single agent and in combination with chemotherapeutic agents used as standard of care therapies in these indications
- Results support development of SY-5609 in combination with chemotherapy in PDAC and/or NSCLC tumors with oncogenic KRAS mutations

SY-5609 induces regressions in KRAS-mutant PDAC PDX models including those derived from heavily pre-treated patients

- SY-5609 antitumor activity was screened in a panel of 8 PDAC PDX models (Table)
- 6 mg/kg QD regimen selected to maximize opportunity for signal detection
  - Well-tolerated regimen associated with strong and sustained tumor growth inhibition and pharmacodynamic changes in ovarian cancer xenografts (ESMO 2021, presentation 14P)
- Regressions observed in 50% (4/8) of models
  - 3/4 models with regressions derived from heavily pre-treated patients
  - Regressions sustained for 2 weeks post drug cessation
- Regimen well-tolerated - 0% average body weight change at end of treatment (day 28) across all models

Summary of SY-5609 antitumor activity in RAS-mutant PDAC PDX models

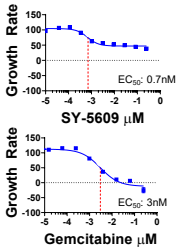
Model ID	TGI (%)	GRI (%)	Clinical Rx	KRAS mutation
ST1300	>100	169	None	G12D
ST1933	>100	139	T, CY, X	NRAS
ST2478	>100	121	F, G, T, X, C	G12D
ST390	>100	119	C, X, G	G12D
ST1250	92	96	None	G12V
ST587	87	86	None	G12V
ST2426	42	32	F, G, T, I	G12D
ST569	8	15	None	G12R

TGI = Tumor Growth Inhibition, GRI = Growth Rate Inhibition
Clinical RX: patient treatments received prior to tumor sample collection for establishment of PDX model
C: capecitabine, CY: cyclophosphamide, F: FOLFIRNOX, G: gemcitabine, I: investigational, T: taxane, X: radiation

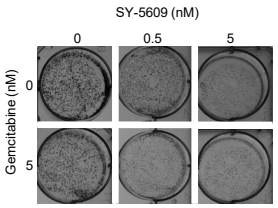
SY-5609 potentiates gemcitabine activity in a KRAS-mutant PDAC preclinical model in vitro and in vivo

SY-5609 potently inhibits growth and potentiates gemcitabine activity in KRAS-G12D-mutant PANC-1 cells in vitro

Proliferation assay (day 5)



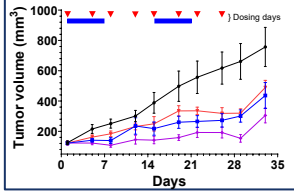
Colony formation assay (day 6)



Results representative of 2 independent experiments

SY-5609 potentiates gemcitabine antitumor activity in PANC-1 xenografts in vivo

- SY-5609 (3 mg/kg) dosed daily 7 days-on/7-days-off (7/7), a schedule with evidence of clinical anti-tumor activity and enhanced tolerability in SY-5609 trial patients (ESMO 2021, 518MO)
  - Similar single agent and combination results observed when SY-5609 dosed continuously for 3 weeks
- In a preclinical CRC PDX model, 3 mg/kg SY-5609 induces *POLR2A* PD responses in tumor tissue to levels associated with regressions (ASCO 2020)
  - Similar *POLR2A* PD responses observed in PBMCs from SY-5609 trial patients at doses ≥ 3mg (ENA 2020)

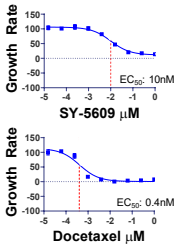


- N=5 per group, mean+/-SEM shown in figure
- All regimens well tolerated, average body weight change on day 29:
  - Vehicle (+5%), SY-5609 (+4%), Gem (-3%), Combo (-1%)

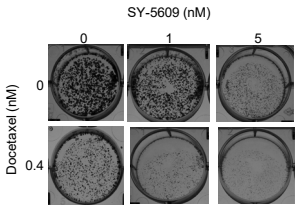
SY-5609 potentiates docetaxel activity in KRAS-mutant NSCLC preclinical models in vitro and in vivo

SY-5609 potently inhibits growth and potentiates docetaxel activity in KRAS-G12S-mutant A549 cells in vitro

Proliferation assay (day 5)



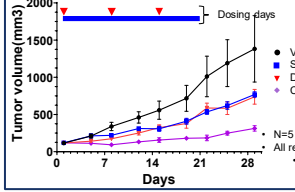
Colony formation assay (day 6)



Results representative of 2 independent experiments

SY-5609 potentiates docetaxel antitumor activity in A549 xenografts in vivo

- SY-5609 3 mg/kg dosed daily on a continuous schedule for 3 weeks
  - SY-5609 7/7 schedule not tested in combination with docetaxel in A549, however 7/7 and continuous schedules induce similar antitumor activities with single agent SY-5609 3 mg/kg QD
- Results consistent with combination activity observed in a KRAS-G12C mutant NSCLC PDX with same SY-5609 regimen and similar docetaxel regimen (10mg/kg, I.V., QW)



- N=5 per group, mean+/-SEM
- All regimens well tolerated, average body weight change on day 21:
  - Vehicle (+11%), SY-5609 (+2%), Doc (+4%), Combo (-3%)

Conclusions

- SY-5609 demonstrates robust single agent antitumor activity in preclinical PDX models of KRAS-mutant PDAC
- SY-5609 potentiates the activity of chemotherapeutic agents in preclinical models of KRAS-mutant-PDAC and -NSCLC at a dose (3 mg/kg) associated with PD changes observed in CRC xenografts that regress on treatment and in PBMCs from SY-5609 trial patients
- SY-5609 (3 mg/kg QD) potentiates gemcitabine antitumor activity in KRAS-mutant PDAC xenografts using an intermittent schedule (7-days-on/7-days-off) associated with preliminary antitumor activity and enhanced tolerability in SY-5609 trial patients; similar results observed with docetaxel in KRAS-mutant NSCLC xenograft models
- Results support clinical evaluation of SY-5609 in combination with gemcitabine in PDAC and with docetaxel in NSCLC
- Tolerability and preliminary clinical activity of SY-5609 in patients with advanced solid tumors, including PDAC, are reported elsewhere (ESMO 2021, presentation 518MO)