Abstract 2862

Presentation 14P

Preclinical Evaluation of Intermittent Dosing Regimens on Antitumor and PD Activity of SY-5609, a Potent and Selective Oral CDK7 Inhibitor, in Ovarian Cancer Xenografts

Liv Johannessen, Wojciech Dworakowski, Maria Rosario, Priyanka Sawant, Nan Ke, Ariel Lefkovith, Anthony D'Ippolito, Matthew Eaton, Susan Henry, Graeme Hodgson
Syros Pharmaceuticals, Cambridge, MA, USA; * All authors are employees and stockholders of Syros Pharmaceuticals; contact: ljohannessen @syros.com

Introduction

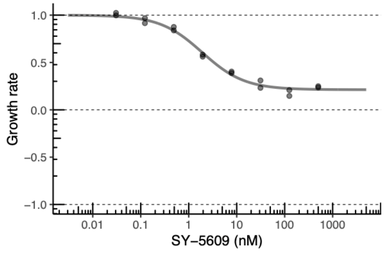
- Selective CDK7 inhibition has been shown to target two fundamental processes in cancer: transcription and cell cycle control
- CDK7 is a key regulator of transcription, through phosphorylation of the CTD of RNA Polymerase II, and cell cycle progression, through phosphorylation of cell cycle kinases CDK1, 2, 4, and 6
- SY-5609 is a potent and selective CDK7 inhibitor in Ph1 clinical development in patients with advanced solid tumors including ovarian cancer (NCT04247126)
- We previously demonstrated SY-5609 antitumor activity in preclinical models of high grade serous ovarian cancer (HGSOC) using a daily continuous dosing regimen
- Here we report on the impact of intermittent SY-5609 dosing regimens on antitumor activity in the OVCAR-3 model of HGSOC
- Results support evaluation of intermittent dosing schedules in patients as a strategy to optimize single agent or combination SY-5609 activity

Methods

- Single agent growth rate (GR) inhibition curve was generated in OVCAR-3 cell line using the GRmetrics package in R (Software Version v1.10.0) after 5 days
- *POLR2A* PD responses were assessed using a custom NanoString nCounter Element XT codeset used to evaluate PD responses in SY-5609 clinical trial patients (ESMO 2021, 518MO)
- Tumor growth inhibition was compared in OVCAR-3 xenografts across a range of SY-5609 doses (1, 3, 6 mg/kg) and schedules (continuous daily [QD], 5d per wk [5/2], and 7d per wk every other wk [7/7])

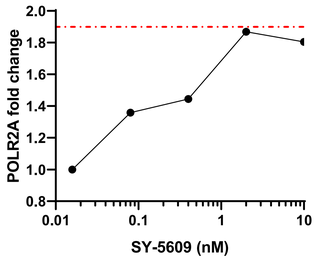
SY-5609-induced growth inhibition of OVCAR-3 cells is associated with induction of *POLR2A* PD changes *in vitro*

Proliferation assay (day 5)



GR_{50} = 1.9nM ± 0.1nM

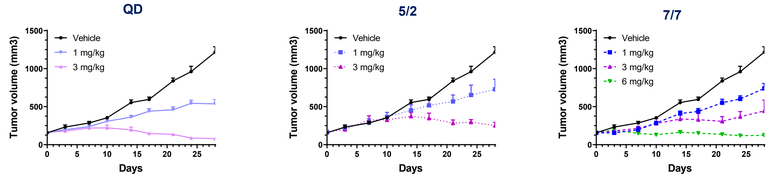
POLR2A PD (28 hours)



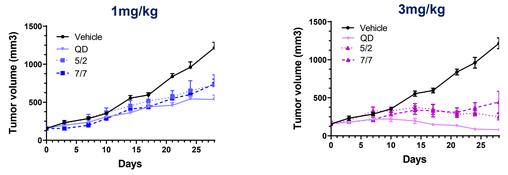
Constant drug exposure, no washout

SY-5609 induces antitumor activity across a range of doses and schedules in OVCAR3 xenografts

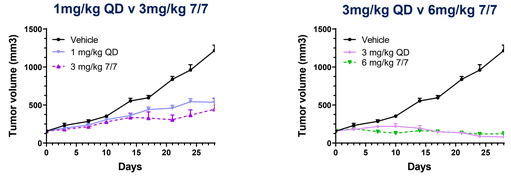
Dose-dependent antitumor activity observed with continuous and intermittent dosing schedules



Comparable antitumor activity observed across dosing schedules within a dose

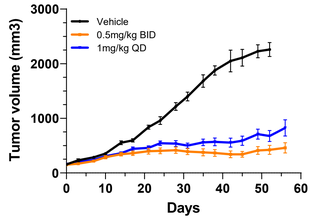


Antitumor activity maintained with higher doses given on a 7/7 schedule



- All dosing regimens were well tolerated, with body weight gain observed throughout treatment

Dose fractionation supports an association between antitumor activity and maintenance of trough SY-5609 levels



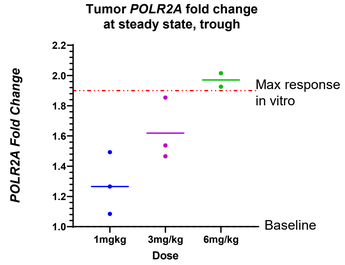
Model Predicted PK parameters

Dose (mg/kg)	Total Daily Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (hr*ng/mL)	C_{trough} (ng/mL)
0.5 mg/kg	1	6.1	93	1.5
1 mg/kg	1	12	104	0.35

- For same daily AUC (0.5 mg/kg BID vs 1 mg/kg QD), higher C_{trough} levels are associated with enhanced antitumor activity
- 1 mg/kg dose induces trough POLR2A PD responses in CRC PDX tissue to levels associated with tumor growth inhibition
  - Similar POLR2A PD responses observed in PBMCs from SY-5609 trial patients at doses ≥ 3mg/day at steady state

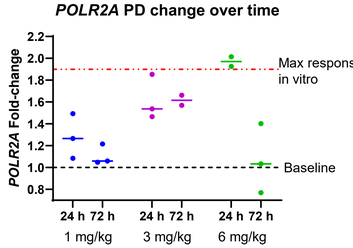
SY-5609 induces dose-dependent PD effects in OVCAR-3 xenograft tissue that are sustained following dosing cessation

Dose-dependent PD changes in tumor tissue at steady state (day 5)



- Samples collected 24h after the day 5 dose, following 5 consecutive days of QD dosing
- 3 mg/kg QD dose achieves ~70% of maximal *POLR2A* response observed at trough in OVCAR-3 cells in vitro (lower left panel)
- Similar dose-dependent PD changes were observed in *E2F1* expression

Sustained PD changes in OVCAR-3 xenograft tissue through 72 hours post dosing, support an intermittent schedule



- *POLR2A* PD response sustained in tumor tissue at ~70% of max through 72 hours post dosing at 3 mg/kg
  - Consistent with sustained POLR2A PD responses in PBMCs from SY-5609 trial patients
- *POLR2A* PD response at 6 mg/kg markedly altered 72 hours post dosing
  - Associated with onset of tumor regression on day 7 at this dose (middle panel, top right) and maximum POLR2A response at steady state trough
- Sustained PD changes from baseline were also observed for *E2F1* expression through 72 hours

Conclusions

- SY-5609 shows robust antitumor activity in preclinical HGSOC xenografts across regimens that integrate higher doses with intermittent dosing schedules
- Antitumor activity was maintained with higher doses given on an intermittent schedule
- *POLR2A* PD effects are sustained in tumor through 72 hours post dosing, supporting an intermittent schedule, and consistent with sustained *POLR2A* PD effects observed in patient PBMCs
- Dose fractionation supports an association between antitumor activity and maintenance of trough SY-5609 levels during a dosing period
- These results support evaluation of intermittent dosing in patients to optimize single agent or combination SY-5609 dose and schedule selection
- Results of SY-5609 intermittent dosing regimens in patients with advanced solid tumors are reported separately (ESMO 2021 mini-oral 518MO)