Abstract 3585

Activity of SY-5609, an oral, noncovalent, potent, and selective CDK7 inhibitor, in preclinical models of colorectal cancer

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Introduction

• Colorectal cancer (CRC) is driven by genetic alterations that result in constitutive activation of oncogenic transcription factors (eg, CCAAT/enhancer-binding protein) and of mitogenic signaling and cell cycle progression (eg KRAS, BRAF).
• CDK7 is a key regulator of transcription, through phosphorylation of the CTD domain of RNA polymerase II, and cell cycle regulation, through phosphorylation of cell cycle kinases CDK2, 4, and 6, suggesting CDK7 inhibitors may be effective in the treatment of CRC, where inhibiting both processes may be important.
• SY-5609 is an oral, non-covalent, potent and highly selective CDK7 inhibitor in phase 1 clinical development (NCT02471276, Abstract TP3362, ASCO 2020)

Methods

In vitro assays and cell cycle: Antiproliferative activity was assessed in SY-480 (KRAS mutant) CRC and WiDr (BRAF mutant) CRC cell lines using the CellTiter-Glo assay. In each dose curve, a log dose–response curve was generated. An IC₅₀ of SY-5609 was calculated for each cell line/compound combination. Additionally, SY-5609 was selected for a panel of 30 CRC cell lines as representative examples of common clinical scenarios. SY-5609 was dosed at 72 HRS using PI/Edu staining via manufacturer protocol and analyzed using FlowJo software.

In vivo models: The relationship between SY-5609 dose, pharmacodynamic (PD) changes in xenograft tumors, tumor growth inhibition (TGI), and body weight change was assessed in a murine xenograft tumor model in vivo. Animals were randomized to treatment or control groups and received SY-5609 or vehicle i.g. for 21 days (QD) at 0 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 9 mg/kg and 12 mg/kg. Tumors were euthanized at 72 HRS using PI/Edu staining via manufacture protocol and analyzed using FlowJo software.

Results

SY-5609 induces dose-dependent tumor growth inhibition and pharmacodynamic effects in tumor tissue in CRC PDX models

Dose-dependent decrease of POLR2A expression in tumor tissue at 24 Hours

Dose-dependent decrease of E2F1 and Cyclin B1 expression in tumor tissue at E10

Conclusions

• SY-5609 potently inhibited proliferation and induced G2/M arrest in KRAS- and BRAF-mutant CRC cell lines in vitro.
• Once daily oral dosing of SY-5609 in a BRAF-mutant CRC PDX model induced dose-dependent tumor growth inhibition (TGI), including regressions that are sustained after treatment discontinuation, at well tolerated doses. dose-dependent TGI is associated with dose-dependent expression changes of cell cycle markers E2F1 and CCNB1 and the transcriptional marker POLR2A.
• Once daily oral dosing of SY-5609 in a panel of 30 CRC PDX models resulted in a 50% TGI in 67% (20/30) and ≥ 90% TGI (deep responses) in 23% (7/30) of models, including in models derived from mutant (KRAS or BRAF) CRC cell lines.
• Sustained regressions observed in 2 BRAF and 1 KRAS mutant CRC model (20/30), including in models derived from human samples.

Putative role for CDK7 inhibition on cell cycle and transcription in CRC

• SY-5609 inhibited proliferation and induced G2/M arrest in BRAF-mutant (WT) and KRAS-mutant (SV-40) CRC cell lines in vitro.
• Once daily oral dosing of SY-5609 in a BRAF-mutant CRC PDX model induced dose-dependent tumor growth inhibition (TGI), including regressions that are sustained after treatment discontinuation, at well tolerated doses, dose-dependent TGI is associated with dose-dependent expression changes of cell cycle markers E2F1 and CCNB1 and the transcriptional marker POLR2A.
• Once daily oral dosing of SY-5609 in a panel of 30 CRC PDX models resulted in a 50% TGI in 67% (20/30) and ≥ 90% TGI (deep responses) in 23% (7/30) of models, including in models derived from heavily pre-treated patients, at well tolerated doses.
• Deep responses were enriched in BRAF mutant (50%, 5/10) vs KRAS mutant or wild-type models (10%, 1/10 each); tumor regressions were observed in 2 BRAF and 1 KRAS mutant model.
• These results highlight the therapeutic potential of SY-5609 in CRC and support the evaluation of SY-5609 in CRC in early phase clinical trials.
• SY-5609 is in phase 1 clinical development for patients with advanced solid tumors including CRC (NCT04247128, Abstract TP3362, ASCO 2020)

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