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Tolerability and preliminary clinical activity of SY-5609, a highly potent and selective oral CDK7 inhibitor, in patients with advanced solid tumors

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Background

SY-5609 is a highly potent inhibitor of CDK7, a key regulator of cell cycle progression and transcription. Initial phase 1 results of SY-5609 in patients (pts) with advanced solid tumors reported proof of mechanism with dose-dependent effects on a pharmacodynamic (PD) gene expression marker *POLR2A* mRNA at 3 mg/day, the maximum tolerated dose (MTD) of the continuous daily dosing schedule. Additional data from the ongoing study, including from intermittent dosing schedules, are reported.

Methods

Doses were escalated (ongoing) above the MTD for continuous dosing in 3 schedules, each with 4-week cycles: 1) once daily (QD) dosing 5 days/week (d/wk), 2) twice daily (BID) dosing 5 d/wk, and 3) QD dosing 7 d/wk every other wk. Select cohorts were expanded to evaluate single agent SY-5609 in specific pt populations and a combination with fulvestrant in hormone receptor positive breast cancer pts. Evaluations included: safety per CTCAE v5.0; clinical activity per RECIST v1.1, tumor markers, and clinical evaluations; and PD marker *POLR2A* induction in peripheral blood mononuclear cells.

Results

As of 3/26/21, 51 pts enrolled, including 9 +fulvestrant. Recently, both QD intermittent dosing schedules cleared dose limiting toxicity (DLT) evaluations at 4 mg/d and 5 mg/d, with activity evaluations and escalation to higher doses ongoing. Single agent SY-5609 AEs of any causality (≥20%) included nausea, diarrhea, fatigue, decreased appetite, and thrombocytopenia; majority were low grade (1/2) and reversible. 30% (11/37) of response-evaluable pts had stable disease (SD) as best response. 6 SD pts had tumor reductions of 8.7%-18.1%, with median 198 d (range: 55-273) on treatment. 1 PDAC pt with prolonged SD (>8 months [ongoing]) had a 72% reduction of CA19-9 (5723 to 1609 U/mL), and 1 ovarian cancer pt had an 84% reduction of CA-125 (1950 to 308 U/mL). Dose dependent *POLR2A* induction was observed on intermittent dosing.

Conclusions

Intermittent dosing of SY-5609 is tolerable above the MTD for continuous dosing with evidence of dose dependent PD effects observed. Early evidence of clinical activity, with durable SD and reduction in tumor size and markers, supports continued dose escalation with intermittent dosing.

Clinical trial identification

NCT04247126; first posted January 29, 2020.

Legal entity responsible for the study

Syros Pharmaceuticals, Inc.

Funding

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Disclosure

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