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Early Evidence of Dose-dependent Pharmacodynamic Activity Following Treatment with SY-5609, a Highly Selective and Potent Oral CDK7 Inhibitor, in Patients with Advanced Solid Tumors

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Background: SY-5609 is an oral, noncovalent, highly selective, and potent inhibitor of CDK7, a key regulator of two fundamental processes important in cancer: transcription and cell cycle control. Preclinical in vivo studies identified a pharmacodynamic (PD) gene expression marker, POLR2A mRNA, associated with SY-5609 dose-dependent tumor growth inhibition (TGI). A phase 1 single-agent dose-escalation study of SY-5609 initiated in January 2020 in patients (pts) with advanced breast, colorectal, lung or ovarian cancer, or solid tumors with Rb pathway abnormalities. Dose escalation of SY-5609 in combination with fulvestrant in hormone receptor positive (HR+) breast cancer pts after CDK4/6 inhibitor treatment failure began in June 2020. We report early results from the initial pts with a focus on tolerability, safety, pharmacokinetics (PK) and PD.

Methods: Pts in dose escalation received daily oral SY-5609 in consecutive 28-day cycles. Safety, including cycle-1 dose-limiting toxicities (DLTs), was evaluated. Serial plasma PK, and PD in PBMCs were obtained on days 1 and 15 in cycle 1. PD responses were measured as changes in normalized POLR2A mRNA expression relative to baseline.

Results: As of May 22, 2020, data were available on 5 pts (2 ovarian/fallopian; 1 CRC; 1 endometrial; 1 breast cancer; with Rb pathway abnormalities in 2/5) enrolled into the first two completed single-agent dosing cohorts at 1 mg/day (n=1) and 3 mg/day (n=4). Four were female, median age was 73 (range 53-76). The median treatment duration was 56 days (range 14-65+). The most common AEs (≥ 2 pts) were nausea, constipation, diarrhea, and fatigue. The majority of AEs were low grade and reversible with no DLTs. At 3 mg, the SY-5609 plasma Cmax on days 1 and 15 occurred at 2-4h. The half-life on day 15 ranged from 14.7 to 23.9 hours. The ratios of Cmax (ng/mL) and AUC 0-8h (ng/mL•hr) on day 15 to day 1 were 1.33 ± 0.55 and 2.29 ± 0.83, respectively, suggesting increased SY-5609 plasma exposure at two weeks. On days 1 and 15, maximum POLR2A expression occurred at 4-8h and SY-5609 dose-dependent changes in average POLR2A expression were observed. The magnitude of POLR2A expression changes increased from day 1 to 15 consistent with the increased SY-5609 plasma exposure.

Conclusions: SY-5609 is a highly selective and potent oral inhibitor of CDK7 in phase 1 development. The increase in plasma exposures of SY-5609 from day 1 to 15 with daily dosing is consistent with the PK half-life and steady-state PK. The dose-dependent changes in POLR2A expression are consistent with data from preclinical in vivo models and provide initial evidence of biological activity that was observed in association with TGI in these models. Current safety data supports continued dose escalation, which is ongoing, including in the SY-5609/fulvestrant combination. Updated data will be presented.
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