Phase III study of eprenetapopt (APR-246) in combination with pembrolizumab in patients with solid tumor malignancies

H. Park1, G. Shingparing2, J. Gao1, A. Mahdipour2, J.S. Starr1, M. Furqan3, P. Singh4, A. Ahmrov1, D. Hicham3, P. Gallagher3, E. Attar3, M. Awad6, S. Das1, E.E. Ilene Dunbrava6

1Oncology Department, Washington University School of Medicine, St. Louis, MO, USA; 2Hematology/Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 3Genitourinary Cancers Program, Phase 1 Investigational Program, Massachusetts General Hospital, Boston, MA, USA; 4Medical Oncology, Mayo Clinic Cancer Centers, Rochester, MN, USA; 5Medical Oncology, Mayo Clinic-Patrick Soon-Shiong Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA; 6Hematology Medical Oncology Department, Mayo Clinic Cancer Center, Phoenix, AR, USA; 7Investigational Cancer Therapeutics Department, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; 8Therapeutic Oncology Research Program, Northern Ireland Cancer Institute, Belfast, United Kingdom; 9Molecular Oncology, Mayo Clinic, Rochester, MN, USA; 10Therapeutic Oncology Treatment Center, Dana Faber Cancer Institute, Boston, MA, USA; 11Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

Background: Eprenetapopt is a small molecule that stabilizes the active form of p53 and increases oxidative stress, resulting in tumor cell apoptosis and ferropotosis and alterations in the tumor microenvironment including immune modulation. In preclinical models, eprenetapopt in combination with anti-PD1 therapy significantly improved tumor response. This study was designed to assess the preliminary safety and efficacy data from the phase 1/2 study of eprenetapopt and pembrolizumab.

Methods: A safety lead-in with a 3+3 dose de-escalation design for patients (pts) with advanced solid tumors with known tumor TP53 mutation status (mutant and WT are included) is followed by expansion cohorts in pts with NSCLC (prior anti-PD1/PDL1 required), gastric/GI (GC) and urothelial cancer (UC) (GC and UC were anti-PD1/PD-L1 required). The primary objective was to establish safety and maximum tolerated dose (MTD) of the combination. Primary endpoints include dose-limiting toxicities (DLTs) and adverse events (AEs).

Results: As of April 7, 2021, 20 pts have been enrolled in the study (6 in the safety cohort and 14 in the expansion cohorts: 2 GC, 2 UC, 10 NSCLC) with 18 pts having at least one DLT. Two MTDs were determined: Pix3 with pembrolizumab 2mg/kg in the early phase 1b/2a cohort and 1mg/pix3 with pembrolizumab 2mg/kg in the early phase 1b/2a cohort. There were no DLTs reported in the safety cohort. The dose of eprenetapopt of 4.5 g/day IV D1-4 and pembrolizumab 200mg IV D3 was established as the RP2D. The most common (4-pts) AEs included nausea (74), abdominal pain (5), fatigue (5), diarrhea (5), dysgeusia (4), dizziness (4), and decreased appetite (3). The majority of advanced grade AEs and SAEs were unrelated and associated with disease progression. There were no treatment discontinuations due to AEs. Two pts with TP53 mutant NSCLC who received prior anti-PO-1/PD-L1 therapy demonstrated reductions in target lesion size of 27% and 8.2%, respectively, at the first disease assessment.

Conclusions: The combination of eprenetapopt and pembrolizumab is safe and tolerable. Early signals of anti-tumor activity are observed. The expansion cohorts of the trial continue to enroll.

Clinical trial identification: NCT04383938.

Legal entity responsible for the study: Aprea Therapeutics.

Funding: Aprea Therapeutics.

Disclosure: H. Park: Financial interests, institutional, sponsored/funded by Aprea Therapeutics. X. Gao: Medical Oncology, Mayo Clinic, Rochester, MN, USA; 2Hematology/Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 3Genitourinary Cancers Program, Phase 1 Investigational Program, Massachusetts General Hospital, Boston, MA, USA; 4Medical Oncology, Mayo Clinic Cancer Centers, Rochester, MN, USA; 5Medical Oncology, Mayo Clinic-Patrick Soon-Shiong Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA; 6Hematology Medical Oncology Department, Mayo Clinic Cancer Center, Phoenix, AR, USA; 7Investigational Cancer Therapeutics Department, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; 8Therapeutic Oncology Research Program, Northern Ireland Cancer Institute, Belfast, United Kingdom; 9Molecular Oncology, Mayo Clinic, Rochester, MN, USA; 10Therapeutic Oncology Treatment Center, Dana Faber Cancer Institute, Boston, MA, USA; 11Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

Background: Disregulated Wnt signaling drives several cancers through effects on proliferation, fibrosis and immune evasion. RXC004 is a novel small molecule inhibitor of the protein-serine O-palmitoyltransferase, PORCN, which is required for post-translational modification of Wnt ligands and downstream signaling. RXC004 has potential for monotherapy efficacy in Wnt pathway activated tumors: ~5% pancreatic and ~8% microsatellite stable colorectal (CRC) cancers with RNF-43 mutations or R-Spondin fusions, and thymus and biliary tract (BTC) cancers with high Wnt ligand activity.

Methods: This open label, 3+3 dose escalation study was one module of a multi-modular adaptive design protocol (NCT03447470). Following a single dose with a 7- day washout, patients received RXC004 once daily in 21-day cycles. The primary objectives were to assess safety and tolerability and define a recommended phase 2 dose of RXC004. Secondary objectives were PK and RECIST response. Pharmacodynamic markers included skin Wnt pathway (Axin2) suppression.

Results: Between 05/02/2018 and 21/06/2021, 25 patients with advanced cancers received 850 doses of RXC004. The first patient, who received 1mg daily, discontinued due to diarrhoea and an asymptomatic clavicle fracture was found on follow up. The half-life (T1/2) and exposure were higher than predicted from preclinical models. The study was paused and restarted at 0.5mg. Subsequently, 1mg, 1.5mg, 2mg and 3mg doses were explored. Patients receiving 3mg dosed 120 mg s.c. monthly to prevent bone adverse events [AEs]. For doses <3mg, the most common treatment related AEs were fatigue, nausea, dysgeusia, vomiting and anorexia. No grade 4/5 AEs or bone fragility events were reported. Exposure was dose proportional and median T1/2 was 14.5h. Exposure above the preclinical model IC50 were observed at all doses, as was Axin2 suppression. Five patients, all with Wnt pathway activated tumours [2 BTC, 1 Thymus, 1 mutRNF43 CRC and 1 RSPD fusion CRC] had stable disease, in one case for up to 26 weeks.

Conclusions: In patients with unselected cancers, RXC004 was safe and tolerated at doses up to 3mg, supporting phase 2 development in selected patients with Wnt pathway activated tumours. Studies will open in 2021.

Clinical trial identification: EudraCT 2017-000720-98.

Legal entity responsible for the study: Redx Pharma Plc.

Funding: Redx Pharma Plc.


1Clinical Research, South Texas Accelerated Research Therapeutics, Grand Rapids, MI, USA; 2Medical Oncology, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA, USA; 3Drug Development Unit, Sarah Cannon Research Institute / Tennessee Oncology, Nashville, TN, USA; 4Termeer Center for Targeted Therapies, Massachusetts General Hospital, Boston, MA, USA; 5Clinical Research, South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; 6Division of Gynecologic Oncology, Hermann Hospital, Houston, TX, USA; 7Oakland Hospital, Oakland, CA, USA; 8Translational Medicine, Syros Pharmaceuticals, Cambridge, MA, USA; 9Computational Biology, Syros Pharmaceuticals, Cambridge, MA, USA; 10Clinical Pharmacology, Syros Pharmaceuticals, Cambridge, MA, USA; 11Clinical Pharmacology, Syros Pharmaceuticals, Cambridge, MA, USA; 12Clinical Science, Syros Pharmaceuticals, Cambridge, MA, USA; 13Clinical Development, Syros Pharmaceuticals, Cambridge, MA, USA; 14Clinical Development, Syros Pharmaceuticals, Boston, MA, USA.

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) mRNA expression marker POU2A 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: (1) 3 dose 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 POU2A 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 tohigher doses ongoing. Single agent SY-5609 AEs of any dose >20% included nausea, diarrhea, fatigue, dehydration, anemia, thrombocytopenia, and panhypothyroidism. The response rate was 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 PDCD with prolonged SD (>8 months [ongoing]) had a 72% reduction of CA-19-9 (5723 to 1609 U/ml), and 1 ovarian cancer pt had an 84% reduction of CA-125 (1950 to 308 U/ml). Dose dependent POU2A 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.


Legal entity responsible for the study: Syros Pharmaceuticals, Inc.

Funding: Syros Pharmaceuticals, Inc.

Disclosure: M. Sharma: Financial Interests, Institutional, Principal Investigator: Alkovo; Financial Interests, Institutional, Principal Investigator: Amgen; Financial Interests, Institutional, Principal Investigator: Apoexian; Financial Interests, Institutional, Principal Investigator: Amgen; Financial Interests, Institutional, Principal Investigator: AstraZeneca; Financial Interests, Institutional, Principal Investigator: Bristol-Myers-Squibb; Financial Interests, Institutional, Principal Investigator: Celgene; Financial Interests, Institutional, Principal Investigator: Cardiff; Financial Interests, Institutional, Principal Investigator: Clovis; Financial Interests, Institutional, Principal Investigator: CytoMx; Financial Interests, Institutional, Principal Investigator: eFFECTOR; Financial Interests, Institutional, Principal Investigator: Eli Lilly; Financial Interests, Institutional, Principal Investigator: Exelixis; Financial Interests, Institutional, Principal Investigator: Formation Biologics; Financial Interests, Institutional, Principal Investigator: Forty Seven; Financial Interests, Institutional, Principal Investigator: Genentech; Financial Interests, Institutional, Principal Investigator: GlaxoSmithKline; Financial Interests, Institutional, Principal Investigator: Inovio; Financial Interests, Institutional, Principal Investigator: Innocent; Financial Interests, Institutional, Principal Investigator: Inhibikin; Financial Interests, Institutional, Principal Investigator: Ikena; Financial Interests, Institutional, Principal Investigator: Imperial; Financial Interests, Institutional, Principal Investigator: Innopharm; Financial Interests, Institutional, Principal Investigator: Invivogen; Financial Interests, Institutional, Principal Investigator: Jounce; Financial Interests, Institutional, Principal Investigator: KKL Pharma; Financial Interests, Institutional, Principal Investigator: Lexicon; Financial Interests, Institutional, Principal Investigator: LIDOG; Financial Interests, Institutional, Principal Investigator: Livzon; Financial Interests, Institutional, Principal Investigator: Macrogenics; Financial Interests, Institutional, Principal Investigator: Merck; Financial Interests, Institutional, Principal Investigator: Mersana; Financial Interests, Institutional, Principal Investigator: Mesoblast; Financial Interests, Institutional, Principal Investigator: Northern; Financial Interests, Institutional, Principal Investigator: NovoCure; Financial Interests, Institutional, Principal Investigator: OncoMed; Financial Interests, Institutional, Principal Investigator: Pﬁzer; Financial Interests, Institutional, Principal Investigator: SanBio; Financial Interests, Institutional, Principal Investigator: Schaefer; Financial Interests, Institutional, Principal Investigator: Shattuck; Financial Interests, Institutional, Principal Investigator: Simony; Financial Interests, Institutional, Principal Investigator: Solaris; Financial Interests, Institutional, Principal Investigator: Syros; Financial Interests, Institutional, Principal Investigator: Taft; Financial Interests, Institutional, Principal Investigator: Tesaro; Financial Interests, Institutional, Principal Investigator: Treadwell; Financial Interests, Institutional, Principal Investigator: QED; B. Bashir: Financial Interests, Institutional, Principal Investigator: Boehringer Ingelheim; Financial Interests, Institutional, Research Grant: Bicycle Therapeutics; Financial Interests, Institutional, Research Grant: Ikena Oncology; Financial Interests, Institutional, Research Grant: Kahr Medical. E. Hamilton: Financial Interests, Institutional, Research Grant: OncoMed; Financial Interests, Institutional, Research Grant: Genentech/Roche; Financial Interests, Institutional, Research Grant: Otsuka; Financial Interests, Institutional, Research Grant: Arbor; Financial Interests, Institutional, Research Grant: Clovis; Financial Interests, Institutional, Research Grant: Silverback Therapeutics; Financial Interests, Institutional, Research Grant: Millenium; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Research Grant: Merck; Financial Interests, Institutional, Research Grant: Pﬁzer; Financial Interests, Institutional, Research Grant: Cyborg; Financial Interests, Institutional, Research Grant: Bayer; Financial Interests, Institutional, Research Grant: Boehringer Ingelheim; Financial Interests, Institutional, Research Grant: Bicycle Therapeutics; Financial Interests, Institutional, Research Grant: Ikena Oncology; Financial Interests, Institutional, Research Grant: Kahr Medical.

https://doi.org/10.1016/j.anonc.2021.08.1039

Volume 32 ■ Issue S5 ■ 2021