Background exoASO-STAT6™ is an investigational therapeutic candidate consisting of exosomes loaded with an antisense oligonucleotide (ASO) targeting STAT6. By leveraging exosome tropism to tumor-associated macrophages (TAM), exoASO-STAT6™ is the first systemically administered exosome designed to selectively silence STAT6 in TAMs, inducing their reprogramming from ‘M2’ immunosuppressive to ‘M1’ proinflammatory phenotype, resulting in the induction of an antitumor immune response and potent monotherapy activity in mouse models. A Phase I study in hepatocellular carcinoma (HCC) patients is currently enrolling.

Methods Here, we evaluated Pharmacokinetics (PK) and Pharmacodynamics (PD) of systemically dosed exoASO-STAT6 in mouse and non-human primates (NHP), identified PD biomarkers with clinical translatability and generated bioinformatic-based rationale for the selection of tumor indications in the clinic.

Results PK analysis in mice and NHP treated with a single IV dose of exoASO-STAT6 (mouse: 0.2-1.5 mg/kg; NHP: 0.3-2.7 mg/kg) suggested rapid clearance of ASO from the plasma within hours. exoASO-STAT6 accumulated in the liver in a dose-proportional manner and was detectable for up to 28 days at all dose levels. Repeated (weekly) administration of exoASO-STAT6 resulted in increased ASO exposure in the liver. PD analysis of STAT6 mRNA expression in liver tissue after a single IV dose showed dose-dependent and durable target gene knockdown (KD) that persisted for up to 28 days with maximal KD between days 4 and 7 in mouse (1.5 mg/kg dose: 69.2±0.7% KD, p<0.0005 vs. control), and at day 9 in NHP (first timepoint measured) (2.7 mg/kg dose: 50±3% KD, p<0.0001 vs. control). The extent of STAT6 KD in the liver is proportional to liver exposure, demonstrating a direct relationship between exoASO-STAT6 dose and PD response. Gene expression analysis from NHP liver showed durable modulation of several genes, including IL-4 receptor (IL4R), a gene directly regulated by STAT6 (day 9, 2.7 mg/kg dose: 58±7% KD, p<0.0001 vs. control). Histological analysis confirmed that STAT6 and IL4R are expressed by TAMs in human HCC tumors, supporting the rationale to use these two biomarkers in the clinic. Analysis of The Cancer Genome Atlas database identified several tumor indications in which high expression of a macrophage-STAT6 signature correlates with poor survival, including HCC, stomach, and bladder cancer (p=0.012, p=0.00056, and p=0.0021, respectively).

Conclusions In summary, we demonstrated that exoASO-STAT6 has a durable PK/PD profile in the liver of preclinical species, identified PD biomarkers with good clinical translational potential and described a rationale for selecting cancer subtypes that could benefit from treatment with exoASO-STAT6.