EXENOKINE-2: A HALF-LIFE EXTENDED NO-α-IL-2 WITH IMPROVED PRECLINICAL PHARMACOLOGICAL PROPERTIES SUPPORTS FIRST-IN-HUMAN CLINICAL DEVELOPMENT

1Lili Cheng*, 1Fan Ye, 1Sandra Chen, 1Jianing Huang, 1Jenny Jiang, 1Henry He, 1Shirley Shi, 1Mingxing Yang, 1Qiang Fu, 1Ark Xia, 1Yudan Hong, 1Wang Xin, 1Karen Yuan, 1Hongchuan Liu, 2Hui Feng, 1Eugene Liu, 2Ziyang Zhong, 1Anwita Biosciences, San Carlos, CA, USA; 2Junshi Pharma, Shanghai, China

Background IL-2 is a critical cytokine driving immune-mediated killing of tumor cells by stimulating both the innate and adaptive immune cells. High-dose IL-2 (aldesleukin) has been approved for the treatment of metastatic melanoma and metastatic renal cell carcinoma, however, the practical use of aldesleukin in the clinic is limited. The short half-life of aldesleukin necessitates a frequent and burdensome treatment schedule for patients. In addition, binding to IL-2Rα on endothelial cells and type 2 innate lymphoid cells is thought to induce severe adverse events associated with vascular leak syndrome. Furthermore, the efficacy of aldesleukin is compromised due to strong activation of immunosuppressive regulatory T cells (Treg) expressing the high-affinity IL-2Rαβγ. To overcome the major limitations of wild-type (WT) IL-2, Exenokine-2 (Exn-2), a fusion protein comprised of a no-α-IL-2 linked to a humanized anti-human serum albumin (HSA) single domain antibody (sdAb), was designed using Anwita’s discovery platform technology.

Methods Binding affinities were determined using Bio-Layer Interferometry. In vitro potency was assessed using a human primary immune cell-based pSTAT5 assay. In vivo efficacies were assessed in MC38 and B16F10 syngeneic as well as N87 and Raji xenograft mouse models.

Results The no-α-IL-2 in Exn-2 is a chimera between IL-2 and IL-15 cytokines. The lack of binding with IL-2Rα resulted in limited activation of Treg while retaining the high potency on NK cells and CD8+ T cells. The addition of an anti-HSA sdAb in Exn-2 resulted in prolonged systemic exposure with a 30-fold longer half-life in mice as compared to WT IL-2. In syngeneic mouse tumor models, Exn-2 showed strong dose-dependent antitumor efficacy as a single agent with up to 95% reduction in tumor growth, as well as an enhanced efficacy with a high rate up to 66% of complete response when combined with an anti-PD-1 monoclonal antibody. In xenograft models of gastric cancer and lymphoma, Exn-2 significantly potentiated the antitumor activity of Trastuzumab and Rituximab, respectively, demonstrating clinical potential as a combination therapy with ADCC-competent antibodies. In cynomolgus monkeys, Exn-2 was well tolerated and induced robust and sustained expansions of lymphocytes and CD8+ T cells while showing negligible effects on eosinophils and Tregs.

Conclusions Collectively, in vivo efficacies from mouse tumor models as well as the desired pharmacodynamic effects and safety profile observed in cynomolgus monkeys support the first-in-human clinical development of Exn-2. IND-enabling studies for Exn-2 is nearing completion, with GMP lot production completed for the Phase 1 study.

Ethics Approval The protocol of animal studies has been reviewed and approved by IACUC