ASKG915 – AN ANTI-PD-1 ANTIBODY-IL-15 PRODRUG FUSION MOLECULE WITH ENHANCED THERAPEUTIC POTENTIALS

Kurt Shanebeck*, Chunxiao Yu, Shiguang Yu, Jieye Sun, Dongfang Wang, Jeanine Luiz, Ming Li, Ray Chuang, Jing Chen, Samantha Luiz, Lynwel Cunanan, Stone Shi, Matt Hu, Yong Wen, Jeff Lu, Yuefeng Lu. AskGene Pharma Inc., Camarillo, CA, USA, Aosaikang Biotherapeutics Co Ltd, Nanjing, China

Background AskGene has established a proprietary cytokine prodrug platform (Smartkine®) to achieve its overarching objective of modulating immune reactions at a disease site in a selective and controlled manner. Cytokines are potent molecules, yet their broad application as therapeutics has been hampered due to short PK, severe systemic toxicity, and narrow therapeutic window. To improve the therapeutic potential of cytokines, AskGene has developed several antibody-cytokine prodrug fusion molecules using its proprietary SmartKine® platform.

Methods The in vitro activities of ASKG915 were evaluated using reporter cell line and PBMC-based assays. Peripheral immune activation was evaluated in a GvHD model with human PBMC-engrafted NSG mice. Anti-tumor activities were tested in a human PBMC-engrafted tumor xenograft model and a syngeneic tumor model. The PK/PD properties and safety profiles of ASKG915 were assessed in non-human primates (NHPs) following three IV injections every two weeks.

Results ASKG915 showed minimal activity prior to protease-dependent activation and significantly enhanced activity after protease-dependent activation in vitro. Specifically, it has significantly higher activities stimulating PD-1+ immune cells, presumably through “cis activation”. In in vivo efficacy studies, it showed similar potency as a reference anti-PD-1-IL-15 fusion molecule (not masked) while having a better safety profile. In addition, in a GvHD study, ASKG915 at 10 mg/kg i.p. induced lower interferon gamma levels in the periphery at Day 4 compared to the reference molecule at 1 mg/kg i.p. These results showed that, compared to the reference molecule, ASKG915 had comparable immune stimulation in the tumor while having significantly reduced immune stimulation in the periphery. In NHPs, ASKG915 demonstrated prolonged and antibody-like PK profiles. More importantly ASKG915 was well tolerated at the highest dosage tested in NHP, with no cytokine release syndrome (CRS) and minimal immune reaction at injection sites.

Conclusions Activated ASKG915 showed selective stimulation for PD-1+ immune cells in in vitro assays with human PBMC. ASKG915 in vivo showed tumor-selective activation compared to a reference molecule. In addition, it had extended antibody-like PK in NHPs and was well tolerated at the highest dosage tested in the GLP PK/PD study. It also showed a significantly expanded therapeutic window. An IND filing is planned in the second half of 2022. To our knowledge, ASKG915 is the first anti-PD-1 antibody-IL-15 prodrug fusion molecule moving into clinical development.

Ethics Approval The use of the animals in the studies have been approved by the ethics committees of the research contract organizations (CRO).