ES005, A HIGH AFFINITY ANTI-LAG3 MONOCLONAL ANTIBODY, INHIBITS THE INTERACTIONS BETWEEN LAG3 AND MULTIPLE LIGANDS AND ENHANCES ANTI-TUMOR ACTIVITY OF T CELLS IN PRECLINICAL MODELS

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Background Lymphocyte-activated gene 3 (LAG3) is a cell surface inhibitory receptor expressed by both activated and exhausted CD4+/CD8+ T cells, as well as regulatory T cells (Tregs). It plays an important role in regulating immune homeostasis with multiple biological activities related to T cell functions and is considered a next-generation immune checkpoint after programmed cell death protein 1 (PD-1) and cytotoxic T-cell lymphocyte antigen-4 (CTLA-4). The first identified LAG3 functional ligand is major histocompatibility complex class II (MHC-II). Recently other LAG3 ligands, like fibrinogen like 1 (FGL1), liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin), and galectin-3, were also found to be responsible for the inhibitory function of LAG3, suggesting that blocking these interactions simultaneously may bring greater clinical benefit in cancer treatment. We have developed a high affinity LAG3 blocking antibody ES005 that inhibits the interactions between LAG3 and multiple ligands and it enhances anti-tumor activity of T cells in preclinical models.

Methods LAG3 binding activity and affinity were evaluated by FACS and surface plasmon resonance system (Biacore). Blocking activity was determined by competition assay. In vitro functional activity was determined by NFAT reporter assay and antigen specific T cell activation assay. In vivo efficacy was evaluated in a syngeneic mouse breast tumor model with human LAG3 knock-in mice. Epitope analysis was performed by ELISA and hydrogen deuterium exchange mass spectrometry (HDX-MS). Lead clone was humanized via CDR grafting and back mutation screening. Non-human primates (NHPs) models were used to assess the safety and pharmacokinetics of the humanized candidate.

Results ES005 specifically recognizes human LAG3 with high affinity. It binds to a unique epitope on LAG3 that is distinct from known competitor molecules. ES005 potently blocks LAG3 binding to multiple ligands (MHC-II, LSECtin, FGL1). ES005 can reverse LAG3-driven inhibition of NFAT reporter gene expression and T cell activation in a dose-dependent manner. In a syngeneic mouse breast tumor model, ES005 significantly inhibited tumor growth in vivo. ES005 has excellent pharmacokinetics and safety profile in NHPs.

Conclusions In summary, anti-LAG3 mAb ES005 is a multiple-ligand blocker and demonstrated potent single-agent activity in in vivo mouse tumor models, indicating great potential to be used as next-generation immune checkpoint inhibitor in cancer treatment. We are currently advancing the development of ES005 into clinical candidate.