426 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.

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