1062 ES009, A LILRB2-SPECIFIC BLOCKING ANTIBODY, REPROGRAMS MYELOID CELLS INTO PRO-INFLAMMATION PHENOTYPE AND POTENTIATES T CELL ACTIVATION

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Background The ITIM-containing inhibitory receptor leukocyte immunoglobulin-like receptor B 2 (LILRB2, also known as ILT4) is predominantly expressed on myeloid-lineage cells, including monocytes, macrophages, dendritic cells and granulocytes, and is emerging as a key immune checkpoint for tumor immunotherapy. Human LILRB2 broadly binds to multiple ligands including classical MHC-I, HLA-G, angiopoietin-like (ANGPTL) family members, myelin-associated glycoprotein (MAG), and contributes to immune suppression in the tumor microenvironment (TME). Accumulating evidence has demonstrated that blocking LILRB2 reprograms tumor-associated myeloid cells and promotes anti-tumor efficacy in combination with PD-1 antibody in clinical setting. In this study, we seek to further investigate LILRB2 biology and have developed a LILRB2 blocking antibody called ES009 with high affinity and specificity that potently reprograms myeloid cells into pro-inflammation phenotype and potentiates T cell activation.

Methods LILR family homologue binding properties were evaluated by ELISA and FACS. Antigen binding affinity was determined by surface plasmon resonance system (Biacore). Blocking activity was determined by competition assay. Functional activity was evaluated by *in vitro* monocyte activation assay, dendritic cell (DC) differentiation assay, macrophage polarization assay, M2 macrophages-T cells (M2-T) co-culture assay, and an *ex vivo* study with malignant ascites in ovarian cancer patients. Epitope analysis was performed by competitive ELISA and hydrogen deuterium exchange mass spectrometry (HDX-MS). Lead clone was humanized via CDR grafting and back mutation screening.

Results ES009 specifically recognizes human LILRB2 with high affinity. It binds to a unique epitope on LILRB2 that is distinct from known competitor molecules. ES009 potently blocks LILRB2 binding to multiple HLA ligands (HLA-A2, HLA-G) as well as non-HLA ligands (ANGPTL1, ANGPTL2, ANGPTL4, ANGPTL7, MAG). Through blocking ligand interaction and receptor activation, ES009 can promote human monocytes and human monocytes derived DCs into a pro-inflammatory status, reprogram human monocyte derived M2 macrophages into pro-inflammatory M1 phenotype, and restore T cell activity from M2 macrophage-mediated suppression. Most importantly, in an *ex vivo* study, ES009 demonstrated very potent ability in reprogramming primary macrophages from malignant ascites of ovarian cancer patients into a pro-inflammatory status.

Conclusions In summary, the anti-LILRB2 mAb ES009 has demonstrated great potential in the reversion of immune suppression in the TME, leading to promotion of anti-tumor immunity. We are currently advancing the development of ES009 into a clinical candidate.

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