

LAE113, A NOVEL TIGIT/PVRIG BISPECIFIC ANTIBODY FOR THE TREATMENT OF CANCERYan Chen*, Xue Li, Ling Jiang, Xiang-Ju Justin Gu. *Laekna Therapeutics, Shanghai, China*

Background TIGIT and PVRIG, which functions as immune checkpoint inhibitor, are novel targets for immune oncology therapy. They bind to their ligands (PVR/CD155 and PVRL2/CD112 respectively) with high affinity and thus block the interaction of these ligands with the activating receptor CD226. TIGIT and PVRIG are expressed on T cells and NK cells and are upregulated in tumors compared to normal tissues, while their ligands are widely expressed on tumor cells and tumor-associated macrophages, which contributes to local suppression of immune-surveillance. Dual blockage of TIGIT and PVRIG by therapeutic antibodies has synergistic anti-tumor effects in various preclinical studies and showed promising results in early clinical trials.

Methods Anti-human TIGIT monoclonal antibodies (mAb) were generated from mouse hybridoma, while anti-human PVRIG Abs were discovered from Alpaca as a single-domain antibody (sdAb). The development of the anti-TIGIT/PVRIG bispecific antibody (bsAb) LAE113 involved using a humanized sequence derived from the lead anti-TIGIT mAb and the anti-PVRIG sdAb. LAE113 was subjected to binding, blocking, and multiple functional assays, along with competitors such as anti-TIGIT mAb (Tiragolumab), anti-PVRIG mAb (COM701), and anti-TIGIT/PVRIG bsAb (SHR-2002), all of which are currently being tested in clinical trials. Additionally, we evaluated the PK profiles of LAE113 in mice and its stability during stress tests.

Results LAE113 is a novel humanized IgG4 bsAb against human TIGIT and PVRIG with sub-nanomolar affinity and strong blocking activities at both protein and cellular levels. It also exhibits cross-reactivity to corresponding cynomolgus targets. In NFAT luciferase reporter assays, LAE113 demonstrated approximately 1.5-fold greater potency than Tiragolumab and about 4-fold higher potency than COM701 in rescuing TIGIT or PVRIG-mediated inhibitory signaling, respectively. Moreover, LAE113 demonstrated superior activity in primary CD8+ T cell and NK cell activation assays compared to existing competitors, highlighting its best-in-class potential. LAE113 also exhibited a synergistic effect when combined with anti-PD-L1 mAb in enhancing IFN- γ secretion from CD8+ T cells. Furthermore, it induced potent NK-mediated cytotoxicity against MOLM13 cells better than the combination of anti-TIGIT and anti-PVRIG mAbs. In the single-dose study, LAE113 exhibited stable PK properties, and it maintained structural integrity and purity in stressful conditions.

Conclusions LAE113 is an extremely potent TIGIT and PVRIG signaling blocker, outperforming existing competitors (Tiragolumab, COM701, SHR-2002 and SIM0348) in modulating T cell and NK cell functions, and exhibiting a favorable developability profile. It significantly enhanced T cell activity when combined with PD-L1 blockade. These findings suggest that LAE113 holds great promise as a candidate for cancer immunotherapy.

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