LAE113, A NOVEL TIGIT/PVRIG BISPECIFIC ANTIBODY FOR THE TREATMENT OF CANCER

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**Background**
TIGIT and PVRIG, which function as immune checkpoint inhibitors, 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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