Background: Tumor infiltrating lymphocytes co-express PD-1 and CTLA-4 at much higher levels compared to normal tissues and peripheral blood cells, thus anti-PD1/CTLA4 bi-specific antibody with a preferential tumor tissue enrichment over normal tissue would contribute to enhanced efficacy and safety. Currently available anti-PD1 and anti-CTLA4 antibodies used in combination therapy are of residual bindings to FcγRs, which mediate antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), leading to compromise on efficacy and safety. Moreover, activated macrophage in tumor microenvironment plays key role in mediating immune suppression by secreting proinflammatory cytokines, such as IL-6. Cadonilimab, also known as AK104, is an IgG1 scaffold Fc-engineered antibody, which is designed to eliminate binding to FcγRs and C1q, and subsequently minimize lymphocyte loss, and antibody dependent cytokine release from macrophage, which associate with irAEs and poor prognosis in immunotherapy. 

Methods: PD-1 and CTLA4 antigen co-binding activity of Cadonilimab was determined by Fortebio and assay of co-culture Cadonilimab with Hoechst33342-labelled Jurkat cells expressing PD-1 and CHO-K1-CTLA4 cells. Binding kinetics of Cadonilimab to C1q, FcγRIa, FcγRIIa_H131, FcγRIIIa_V158 and FcγRIIIa_F158 were measured by Fortebio. ADCC, ADCP and CDC activities were determined in cellular assays. IL-6 and IL-8 from macrophage were detected in a assay of human macrophage and CHO-K1-PD1-CTLA4 cells co-culture.

Results: Cadonilimab binds to the antigens PD-1 and CTLA-4 simultaneously, and as shown in figure 1, Cadonilimab crosslinks cells expressing CTLA-4 and PD-1. AK104 can crosslink cells expressing CTLA-4 with those expressing PD-1 (figure 1). Cadonilimab exhibited no binding to FcγRIa, FcγRIIa_H131, FcγRIIIa_V158, FcγRIIIa_F158 or C1q (table 1), eliciting no apparent ADCC, ADCP or CDC (figure 2).
Cadonilimab induced no remarkable IL-6 or IL-8 release by human macrophage compared with combination of nivolumab and ipilimumab (figure 3). Clinical trials of Cadonilimab as monotherapy, in combination with chemotherapy or tyrosine kinase inhibitor, such as Lenvatinib and Anlotinib, to treat metastatic cervical cancer (NCT04380805), gastric adenocarcinoma/gastroesophageal junction adenocarcinoma (NCT04728321), non-small cell lung cancer (NCT04647344) and hepatocellular carcinoma (NCT04444167) are ongoing, and a promising efficacy and acceptable safety profile were observed.

Conclusions Cadonilimab, an IgG1 antibody with Fc-engineering, exhibits neither Fc effector functions including ADCC, ADCP, CDC, nor activating macrophage to secret IL-6 or IL-8. Possible tumor tissue preferential retention of Cadonilimab over conventional anti-PD-1 and anti-CTLA-4 antibodies noted above could potentially lead to better safety profile.

REFERENCE


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