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Penpulimab, an IgG1 anti-PD-1 antibody with Fc-engineering to eliminate effector functions and with unique epitope and binding properties

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Background

Currently marketed anti-PD-1 antibodies are typically IgG4 isotype, of which bindings to FcγRs and CH3 region instability might lead to compromise on efficacy and safety. Penpulimab is a humanized IgG1 anti-PD-1 antibody engineered at the Fc region to eliminate binding to FcγRs and C1q, and thus avoid antibody dependent cell-mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) to minimize lymphocyte loss, and to avoid antibody dependent cytokine release (ADCR) such as IL-8 and IL-6, which are known to associate with irAEs and poor prognosis in checkpoint blocking immunotherapy.

Methods

Binding kinetics of penpulimab to C1q, FcγRIa, FcγRIIa_H131, FcγRIIa_R131, FcγRIIb, FcγRIIIa_V158 and FcγRIIIa_F158 were measured by Fortebio. ADCC, ADCP and CDC activities were determined in cellular assays. IL-8, IL-6 from macrophage, and IFN-γ and IL-2 from PBMCs were detected by ELISA. Binding kinetics of penpulimab to human PD-1 was determined by Biacore, and epitope/paratope mapping of PD-1/penpulimab was investigated using X-ray crystallography.

Results

Penpulimab exhibited no binding to FcγRIa, FcγRIIa_H131, FcγRIIb, FcγRIIIa_V158, FcγRIIIa_F158 or C1q, and eliciting no apparent ADCC, ADCP or CDC. Additionally, penpulimab induced no remarkable IL-6 and IL-8 release by macrophages in contract to large amount of these cytokines induced by anti-PD-1 antibodies with IgG4 isotype. Unexpectedly, penpulimab is shown in the co-crystal study to bind to human PD-1 *N*-glycosylation site at N58. This may contribute to a unique slow off-rate of penpulimab binding to PD-1. Thus, penpulimab showed a slower PD-1 binding off-rate (9.51E-05/s) compared to nivolumab (2.43E-04/s) and pembrolizumab (2.80E-04/s). Moreover, penpulimab significantly stimulated IL-2 and IFN-γ secretion in mix lymphocyte reaction, indicating strong T cells activation.

Conclusions

Penpulimab, a PD-1 antibody with IgG1 isotype and Fc engineering, exhibits no Fc receptor mediated effector functions including ADCC, ADCP, and ADCR, and has robust T cell stimulating activity via blocking of PD-1.

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Disclosure

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