PDL1-targeted CD28 costimulatory bispecific antibodies enhance T cell activation in solid tumors

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Introduction

- T cells in the tumor microenvironment require TCR/MHC engagement and costimulatory receptor engagement to achieve complete activation.
- CD28 is a classical costimulatory receptor expressed on T cells, including stem cell-like memory T cells, that has recently been shown to be important for patient response to checkpoint blockade.
- Tumor cells lack expression of CD28 ligands, so we hypothesized that activation of CD28 signaling at the T cell/tumor cell interface could enhance anti-tumor activity.
- We designed PDL1 x CD28 bispecific antibodies that provide CD28 costimulation in the presence of PDL1 and TCR engagement.
- As PDL1 signaling has been shown to directly inhibit CD28 costimulation, this novel bispecific modality has potential to promote CD28 costimulation while simultaneously preventing the suppression of the same signal.

Concept: PDL1 x CD28 bispecific antibody provides CD28 costimulation with built-in PD(L)1 blockade

| Potential superiority to PDL1 blockade | Combines with CD3 engagers | Combines with approved aPD1 |

1. XmAb® heterodimeric Fc platform allows for well-behaved bispecific antibodies

Antagonistic αPDL1
DC: T cell MLR

Non-superagonist μCD28
Air-Dried Stebbings Assay

PDL1 x CD28 XmAb Bispecific

- Highly stable (FcγR interactions eliminated)
- FcγR interactions enhanced

2. PDL1 x CD28 enhances the activity of TAA x CD3 bispecifics

| PDL1 x CD28 enhances the activity of TAA x CD3 bispecifics in the presence of PDL1 |

3. PDL1 x CD28 enhances native TCR/MHC-I interaction and promotes strong anti-tumor activity in a solid tumor model

PDL1 x CD28 enhances T cell / APC interaction in DC: T cell MLR

Mechanism-based PK/PD patient model predicts intratumoral T cell costimulatory activity and consistent PDL1 blockade

| High purity | FcγR interactions eliminated |

4. PDL1 x CD28 mechanism-based PK/PD modeling and cynomolgus monkey PK suggest a patient dosing schedule consistent with typical checkpoint inhibitor regimens

Mechanism-based PK/PD patient model predicts intratumoral T cell costimulatory activity and consistent PDL1 blockade

| Increasing dose level | Central / Peripherial | Tumor compartments included |

Summary

- PDL1 x CD28 XmAb bispecific antibodies were engineered to costimulate CD28 while also blocking PDL1 and were evaluated in vitro and in vivo.
- PDL1 x CD28 enhanced the activity of TAA x CD3 bispecifics and native TCR/MHC-I interaction, and promoted an anti-tumor response in a mouse solid tumor model.
- PDL1 x CD28 was well tolerated in cynomolgus monkeys and its compelling pharmacological properties suggest further investigation.