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

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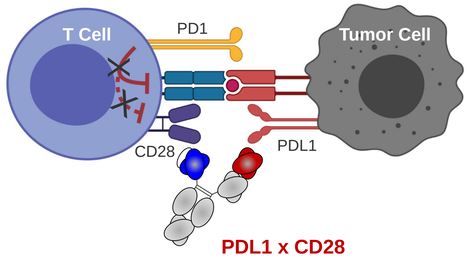
Abstract #698

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 (T_{scm}), a population 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 PD(L)1 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

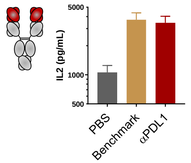
❖ Potentially superior to PD(L)1 blockade ❖ Combines with CD3 engagers ❖ Combines with approved αPD1

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

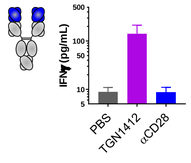
Fc substitutions promote heterodimer formation and facilitate purification by standard methods such as Protein A + ion-exchange chromatography

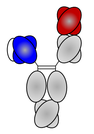
Antagonistic αPDL1 + Non-superagonist αCD28

DC : T cell MLR



Air-Dried Stebbings Assay

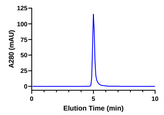




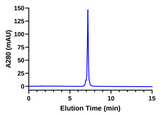
PDL1 x CD28 XmAb Bispecific

- Highly stable αCD28 scFv (T_m ~ 78 °C)
- Xtend™ substitutions to enhance half-life
- FcγR interactions eliminated

Favorable solution properties (SEC)

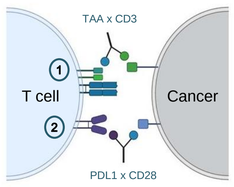


High purity bispecific (IEX)

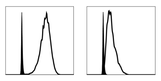


2. PDL1 x CD28 enhances the activity of TAA x CD3 bispecifics

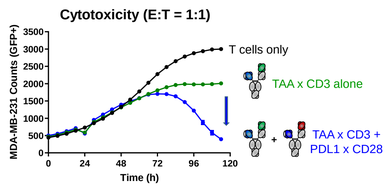
PDL1 x CD28 enhances the activity of TAA x CD3 bispecifics in the presence of PDL1



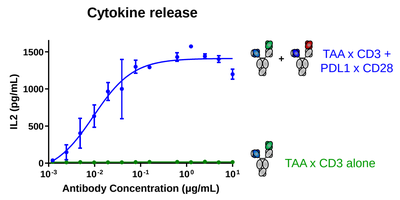
MDA-MB-231 breast cancer cell line



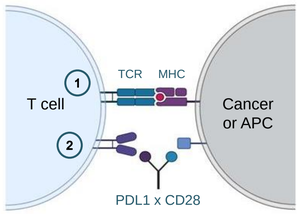
Cytotoxicity (E:T = 1:1)



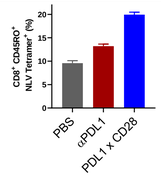
Cytokine release



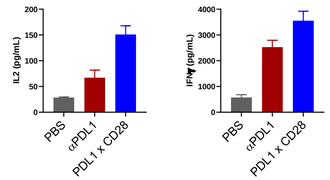
3. PDL1 x CD28 enhances native TCR/MHC-I interaction and promotes strong anti-tumor activity in a solid tumor model



PDL1 x CD28 induces expansion of CMV reactive T cells targeting NLV-loaded MDA-MB-231 cells

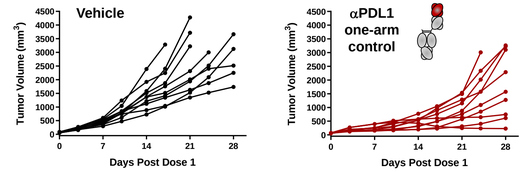


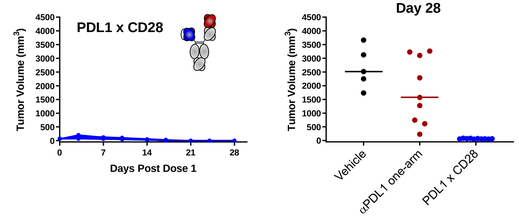
PDL1 x CD28 enhances T cell / APC interaction in DC : T cell MLR



hPDL1-MC38 syngeneic model in hCD28 mice

PDL1 x CD28 inhibits tumor growth more effectively than αPDL1 control

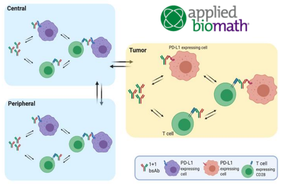




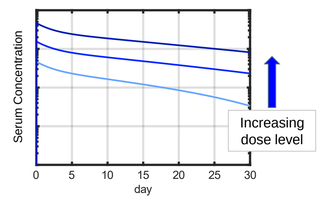
4. PDL1 x CD28 mechanism-based PK/PD modeling and cynomolgus monkey PK suggest a patient dosing schedule consistent with typical checkpoint inhibitor regimens

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

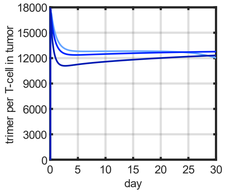
Central / Peripheral / Tumor compartments included



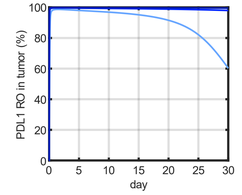
Linear PK at dose levels consistent with typical checkpoint inhibitor regimens



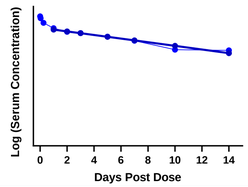
Trimer formation in the tumor indicating costimulation



Consistent blockade of PDL1



PDL1 x CD28 was well tolerated in cynomolgus monkeys and exhibited favorable pharmacokinetics



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 preclinical activity warrants further investigation.

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