Simultaneous checkpoint-checkpoint or checkpoint-costimulatory receptor targeting with bispecific antibodies promotes enhanced human T cell activation

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Introduction

- Tumor infiltrating lymphocytes (TILs) express multiple immune checkpoints and costimulatory receptors (Matsuzaki *et al* PNAS 2010, Fourcade *et al* Cancer Res 2012, Gros *et al* JCI 2014).
- XmAb bispecifics combine dual-targeting of PD1 and CTLA4 (XmAb20717), CTLA4 and LAG3 (XmAb22841), and PD1 and ICOS (XmAb23104) in a single antibody to achieve TIL-specific immune activation.
- Targeting of multiple immune targets with such bispecific antibodies can potentially improve the therapeutic index of combination immunotherapies and reduce treatment-associated costs.

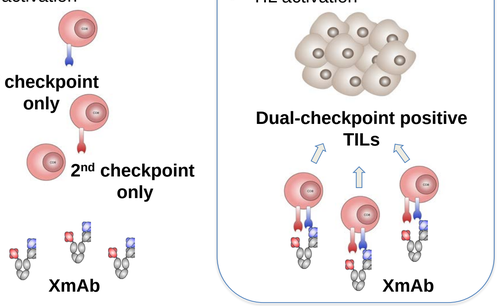
Summary

- TIL-targeting XmAb bispecifics promote T cell activation and proliferation in preclinical models.
- Compelling ex vivo and in vivo data support the clinical development of XmAb20717, XmAb23104 and XmAb22841.
- IND filings for these bispecific antibodies are anticipated in 2018.

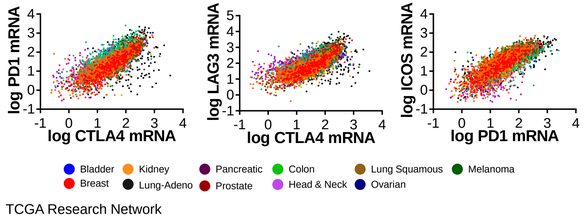
TIL-specific targeting with XmAb bispecifics

Periphery
- Weak monovalent interactions
- No activation

Tumor Environment
- Strong bivalent interactions
- TIL activation



TILs co-express multiple checkpoints: PD1 & CTLA4, CTLA4 & LAG3, and PD1 & ICOS



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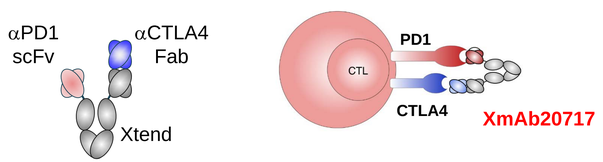
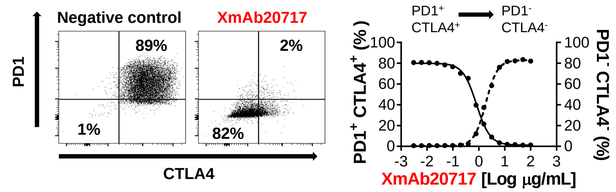
Dual Checkpoint Blockade

XmAb20717



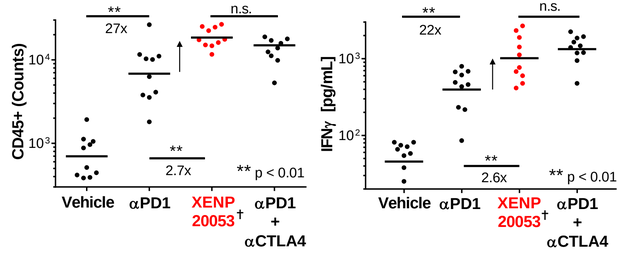
XmAb20717 selectively binds PD1/CTLA4 dual-positive cells

Receptor occupancy of 293T cells co-expressing PD1 and CTLA4



XmAb20717 enhances *in vivo* human T cell activation similarly to combination therapy

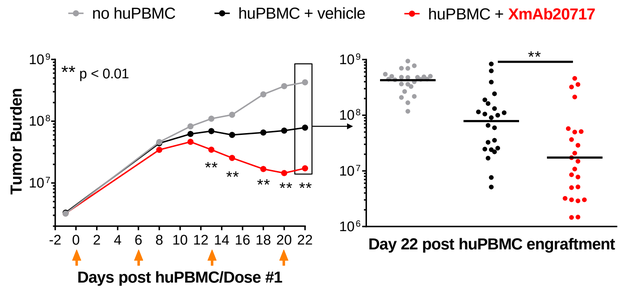
NSG mice engrafted with human PBMC



† XmAb20717 analog without half-life extension (Xtend) mutations

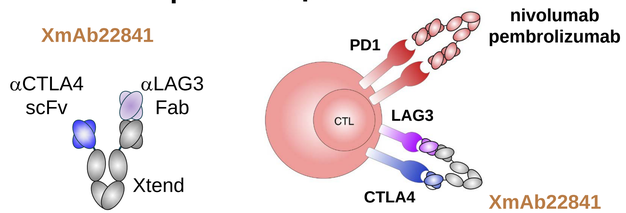
XmAb20717 enhances allogeneic anti-tumor activity

NSG mice engrafted with human PBMC and KG1a-luciferase cells



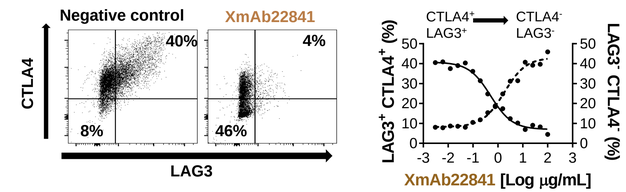
Triple Checkpoint Blockade

XmAb22841



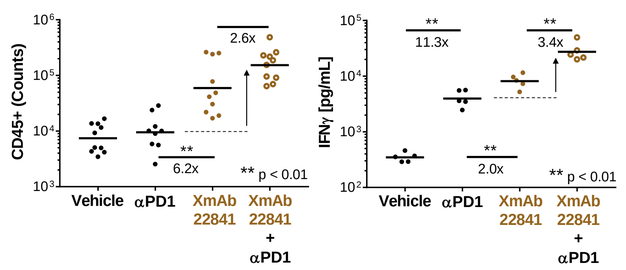
XmAb22841 selectively binds LAG3/CTLA4 dual-positive cells

Receptor occupancy of 293T cells co-expressing CTLA4 and LAG3



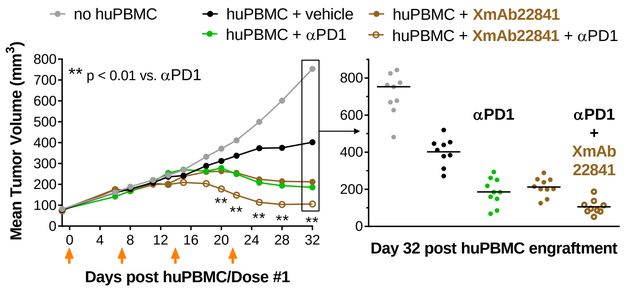
Triple checkpoint blockade significantly enhances *in vivo* human T cell activation

NSG mice engrafted with human PBMC



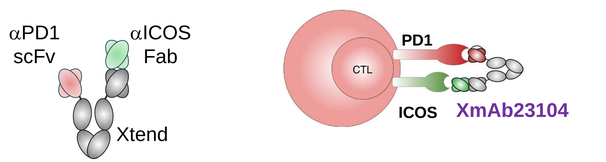
XmAb22841 enhances allogeneic anti-tumor activity and combines productively with PD1 blockade

NSG engrafted with human PBMC and subcutaneously engrafted with MCF7 cells

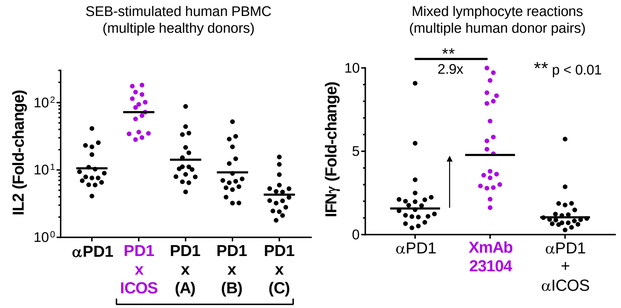


Checkpoint Blockade + T Cell Costimulation

XmAb23104

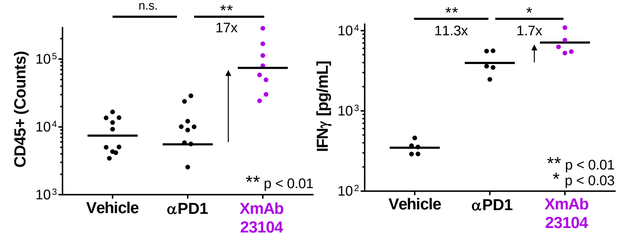


PD1 x ICOS bispecific antibodies were identified in empirical screens for synergistic activities



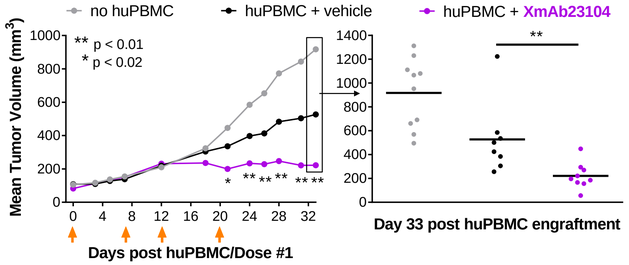
XmAb23104 enhances human T cell activation and proliferation *in vivo*

NSG mice engrafted with human PBMC



XmAb23104 enhances allogeneic anti-tumor activity

NSG mice engrafted with human PBMC and subcutaneously engrafted with MDA-MB-231 cells



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