

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

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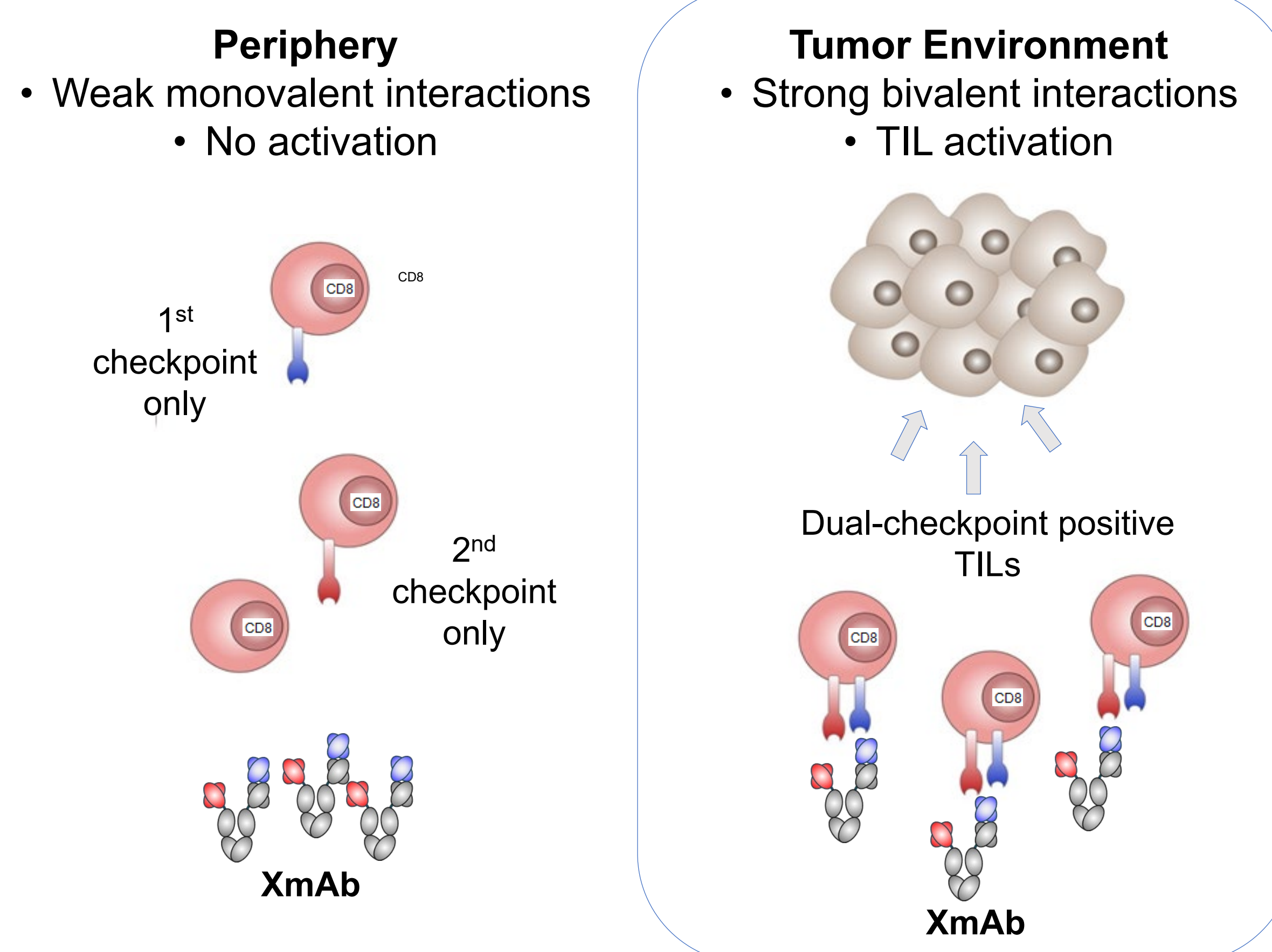
Introduction

- Tumor-infiltrating lymphocytes (TILs) express multiple immune checkpoints and costimulatory receptors.
- 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 bispecific antibodies may improve the therapeutic index of combination immunotherapies and should reduce treatment-associated costs.

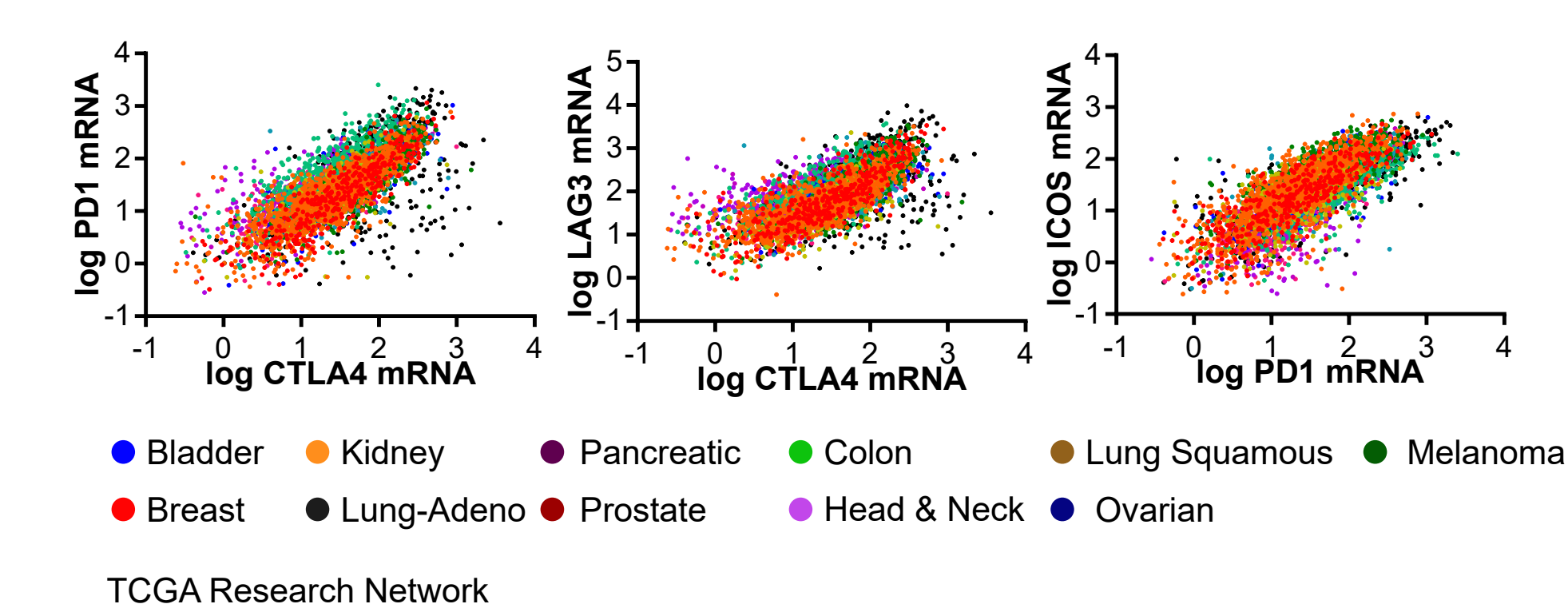
References

Matsuzaki *et al* PNAS 2010
 Fourcade *et al* Cancer Res 2012
 Gros *et al* JCI 2014

TIL-specific targeting with XmAb bispecifics



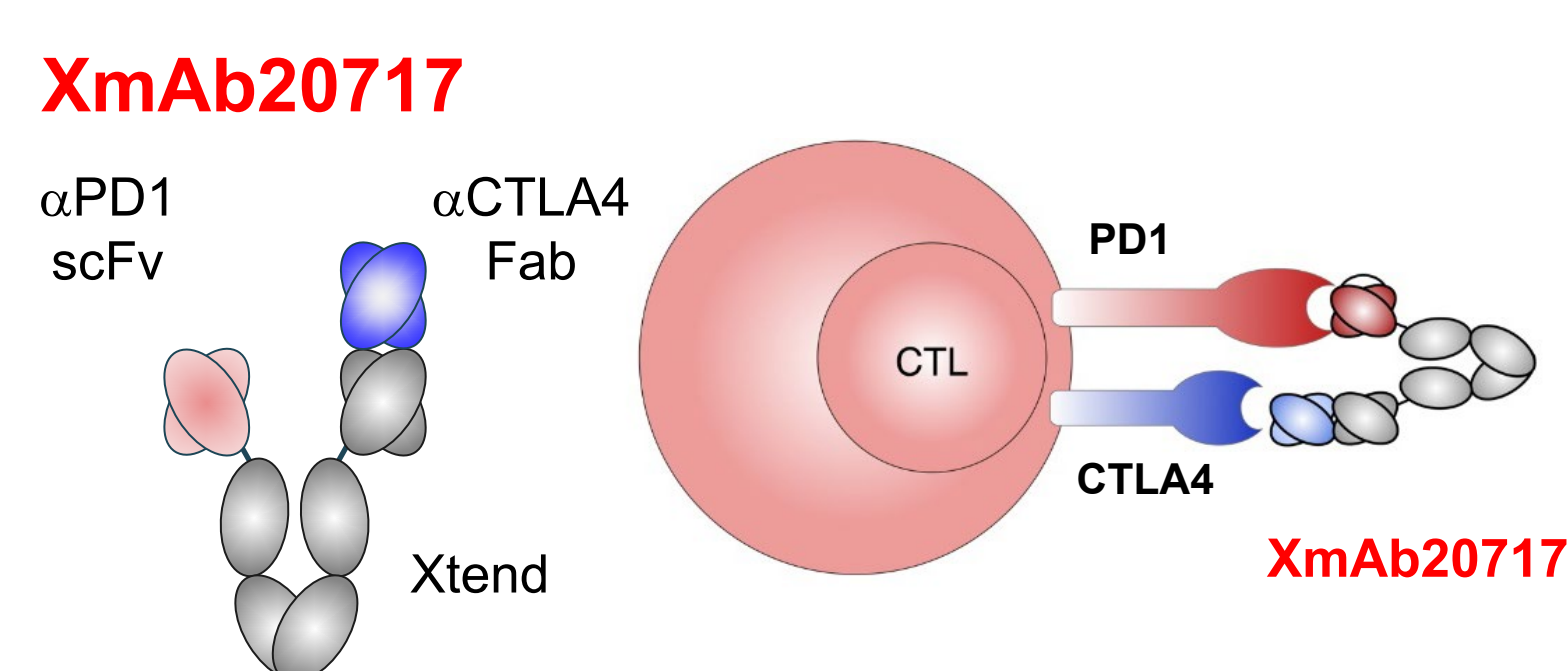
TILs co-express multiple checkpoints



Summary

- TIL-targeting XmAb bispecifics promote T cell activation and proliferation in preclinical models.
- Compelling in vitro and in vivo data support the clinical development of multiple bispecific antibodies.
- XmAb20717: phase 1 dose escalation (DUET-2)
- XmAb23104: open IND
- XmAb22841: anticipated IND filing 2018

Dual Checkpoint Blockade

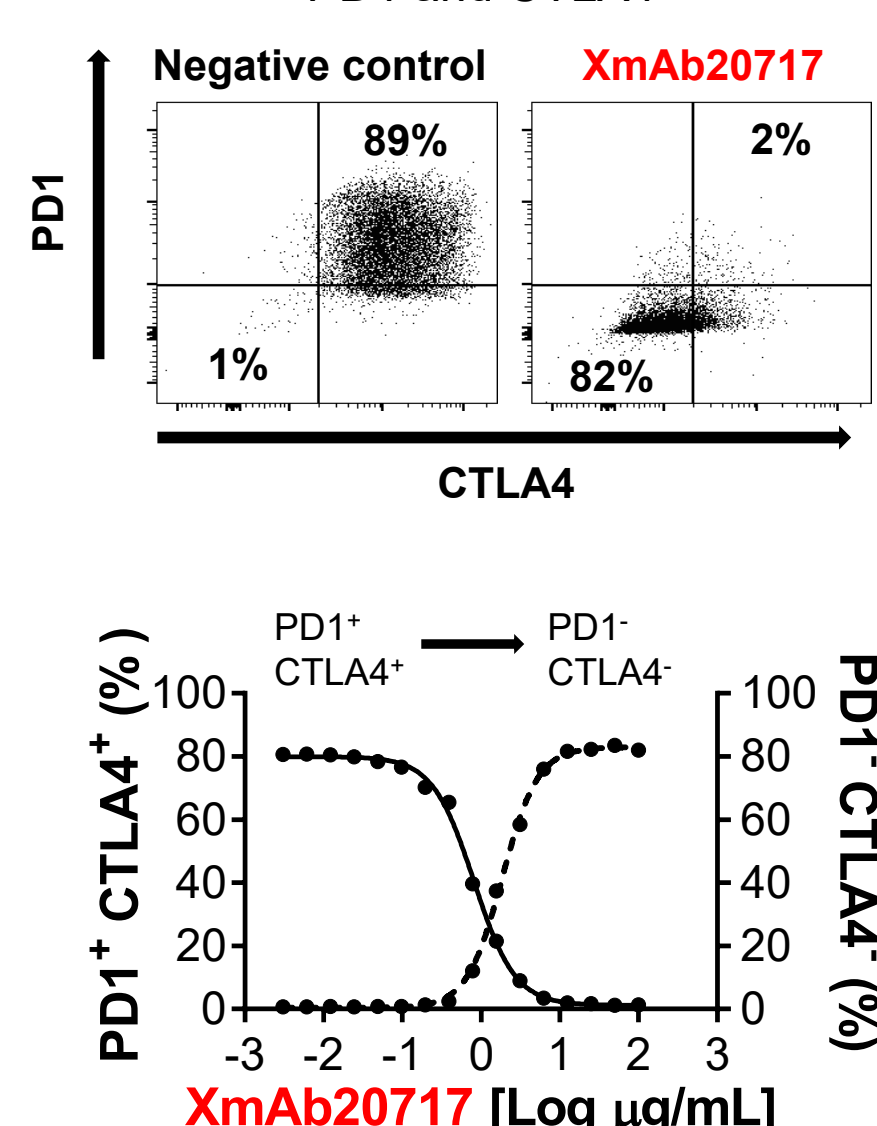


A Study of XmAb20717 in Subjects With Selected Advanced Solid Tumors (DUET-2)

ClinicalTrials.gov Identifier: NCT03517488

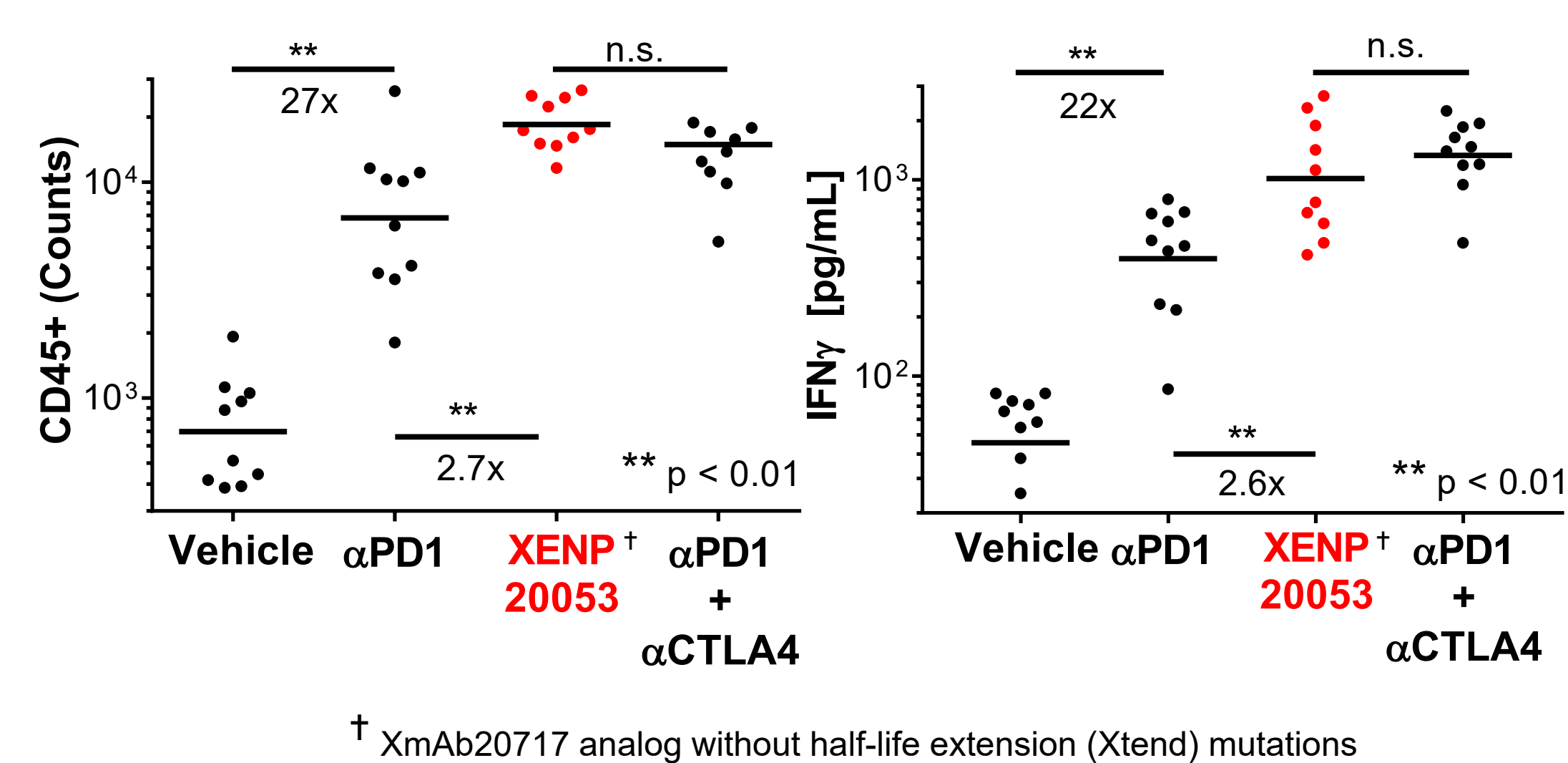
XmAb20717 selectively binds PD1/CTLA4 double-positive cells

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



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

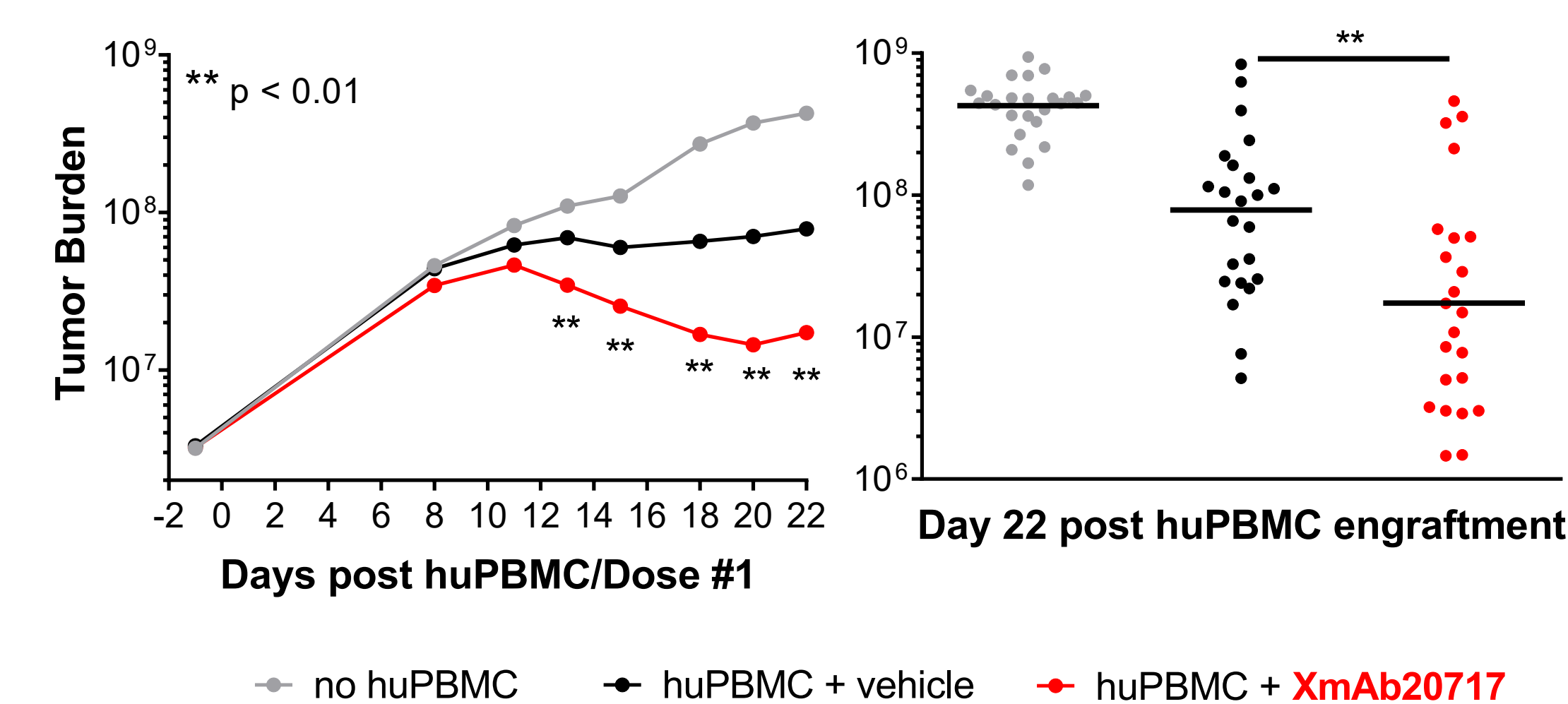
NSG mice engrafted with human PBMC



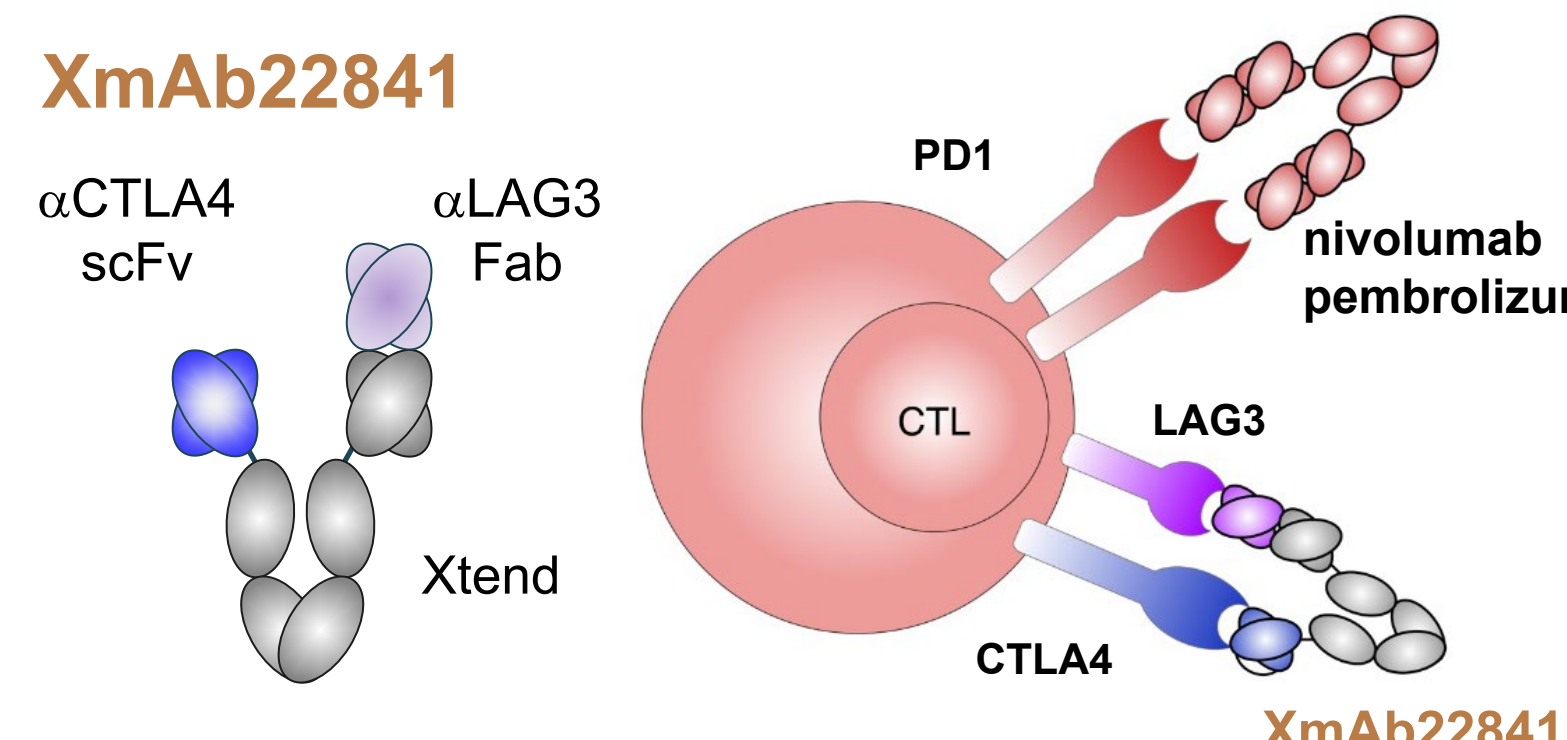
† XmAb20717 analog without half-life extension (Xtend) mutations

XmAb20717 enhances allogeneic anti-tumor activity

NSG mice engrafted with human PBMC and KG1a-luciferase cells



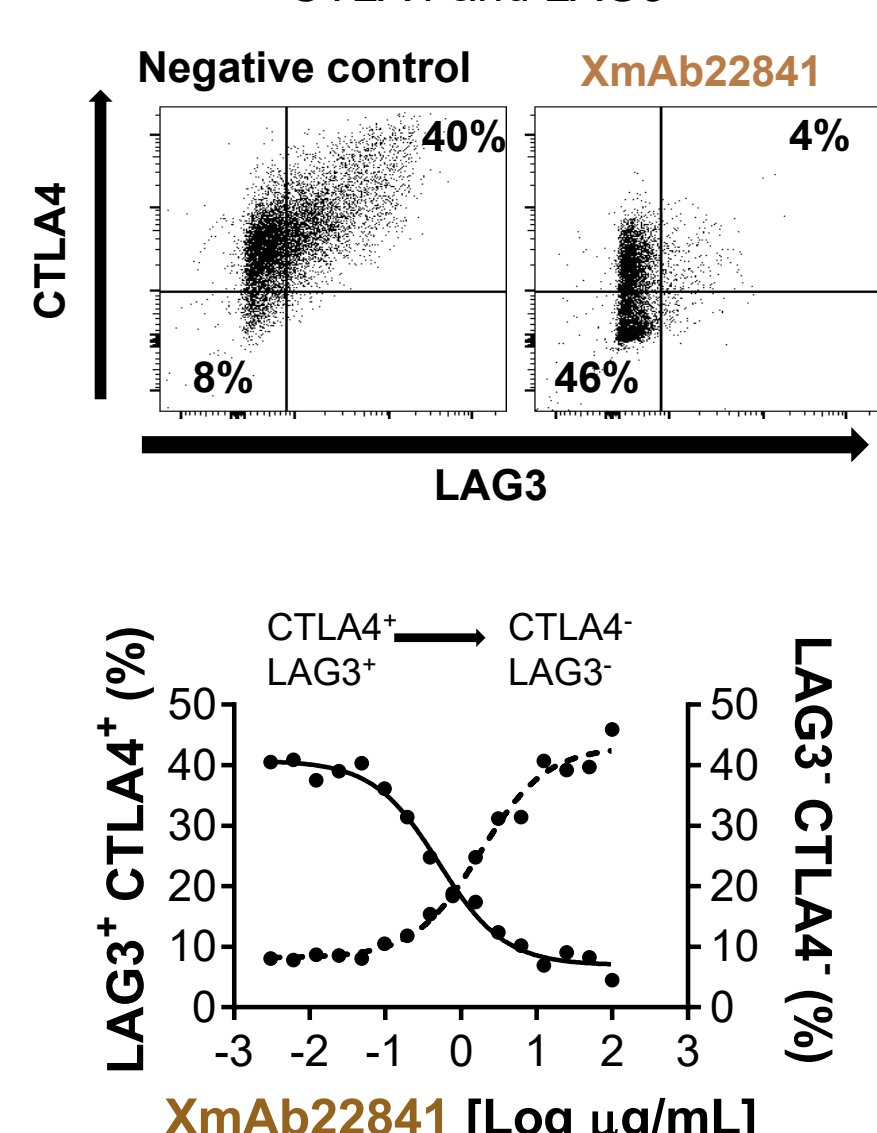
Triple Checkpoint Blockade



IND filing anticipated 2018

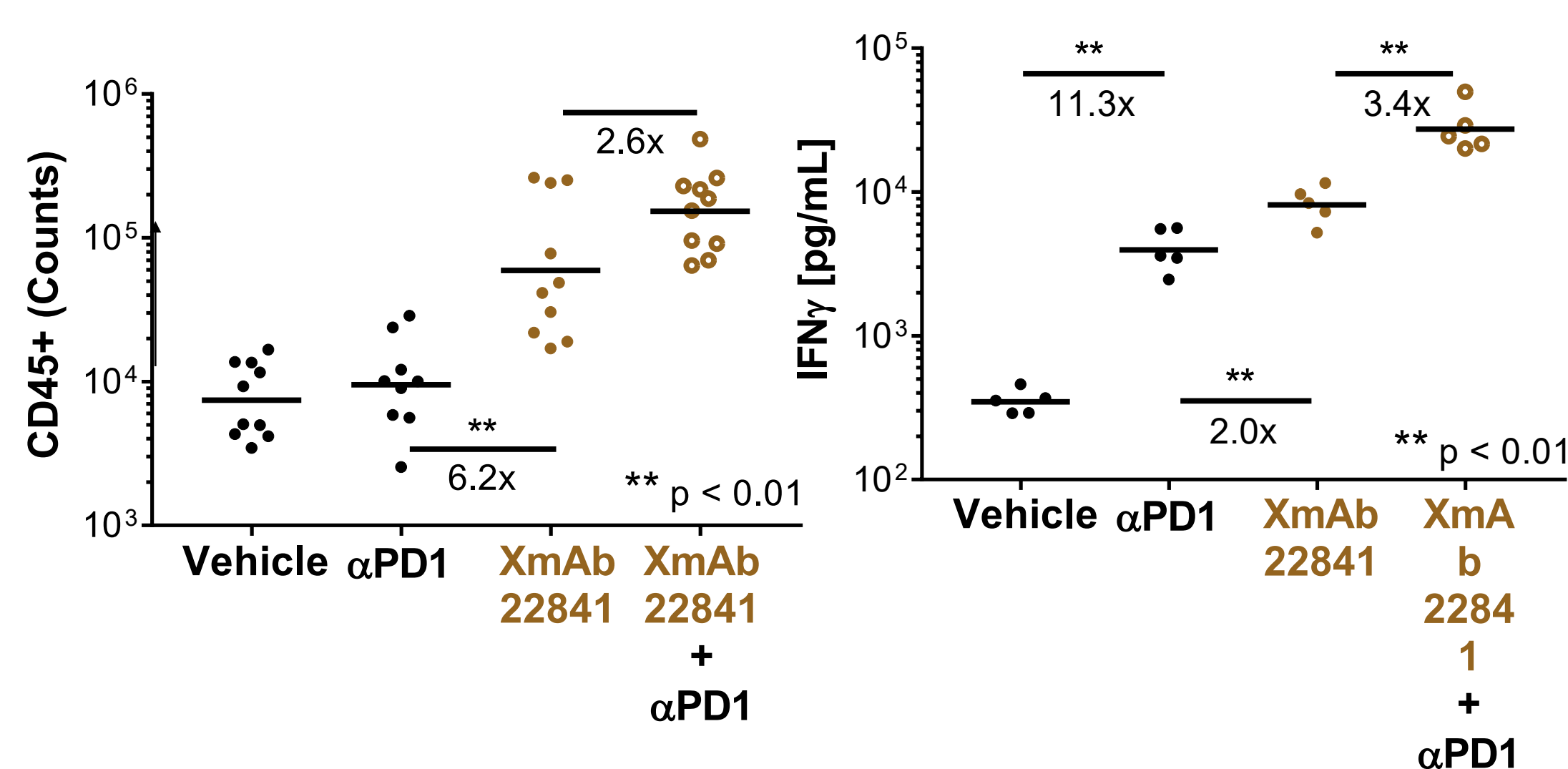
XmAb22841 selectively binds LAG3/CTLA4 dual-positive cells

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



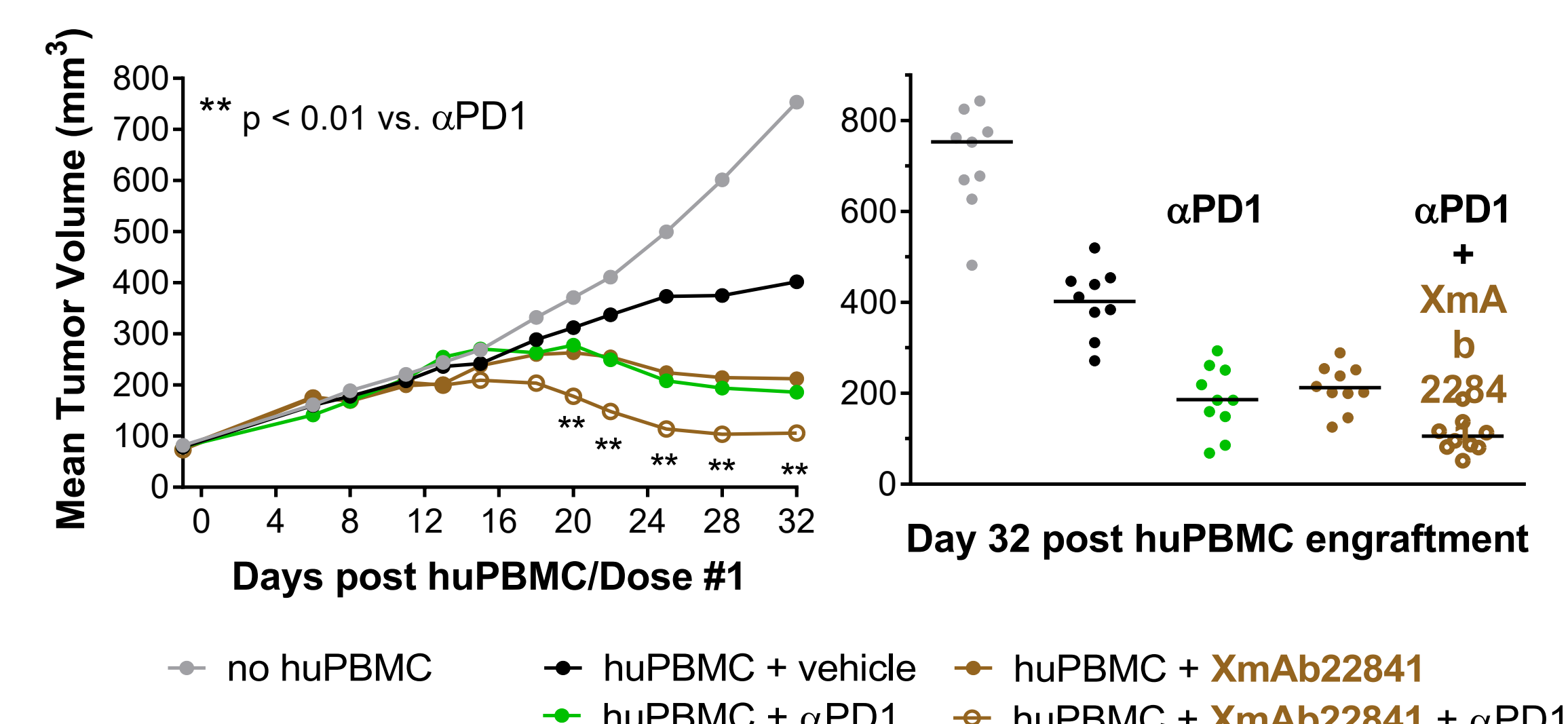
Triple checkpoint blockade significantly enhances *in vivo* human T cell activation

NSG mice engrafted with human PBMC

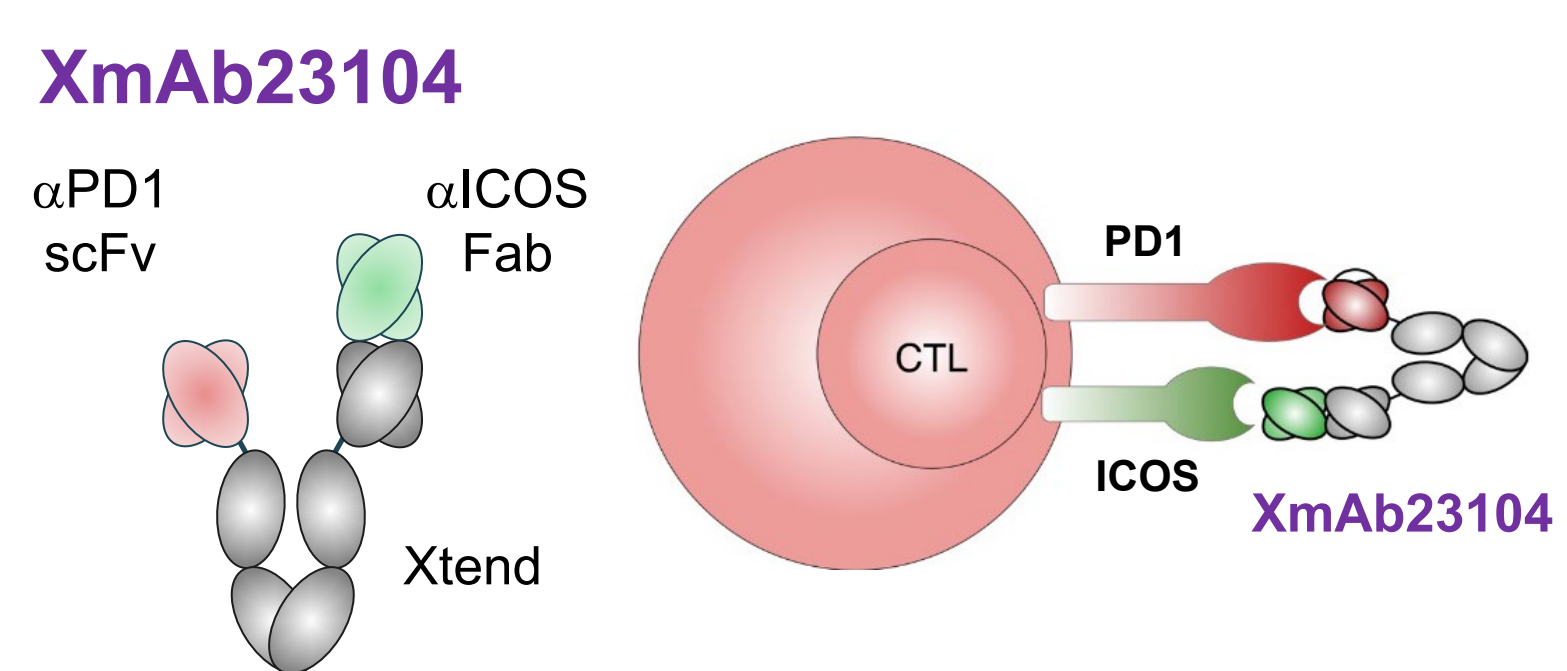


XmAb22841 enhances allogeneic anti-tumor activity and combines productively with PD1 blockade (triple checkpoint blockade)

NSG engrafted with human PBMC and subcutaneously engrafted with MCF7 cells



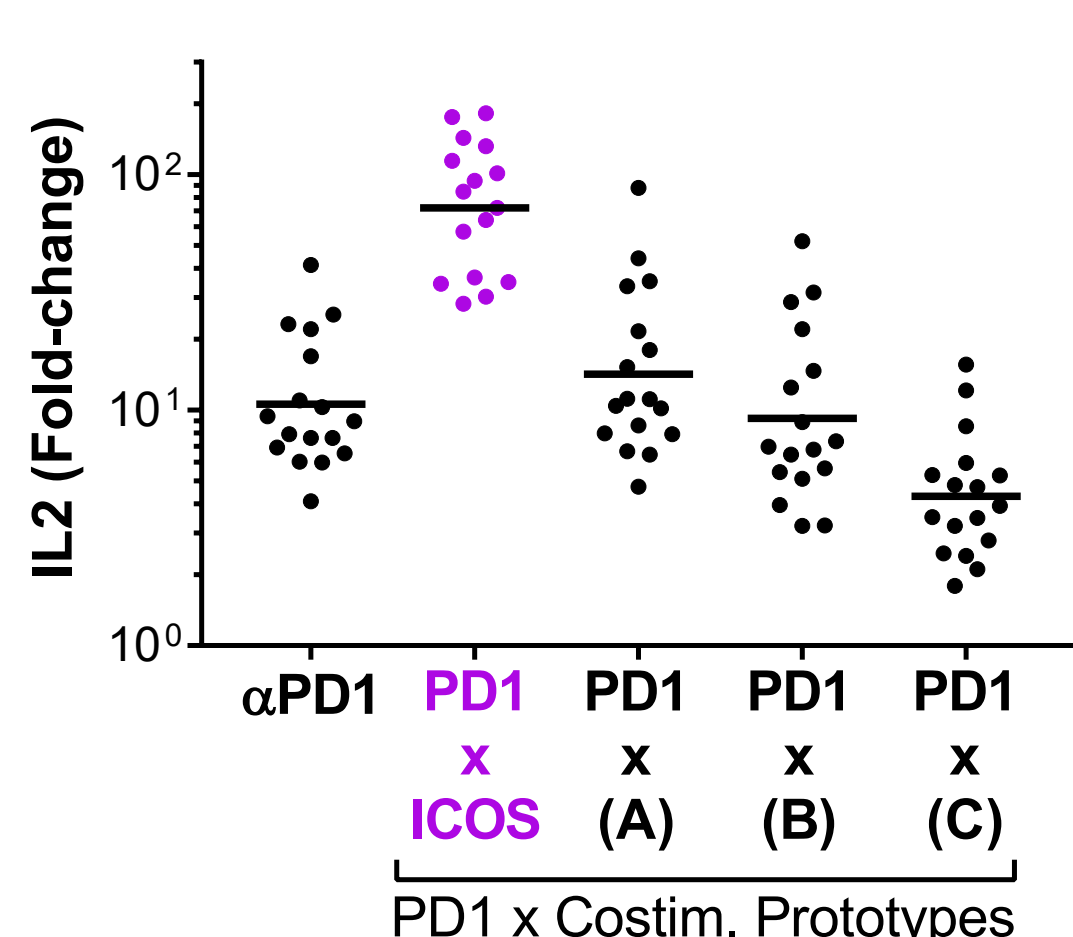
Checkpoint Blockade + T Cell Costimulation



IND open

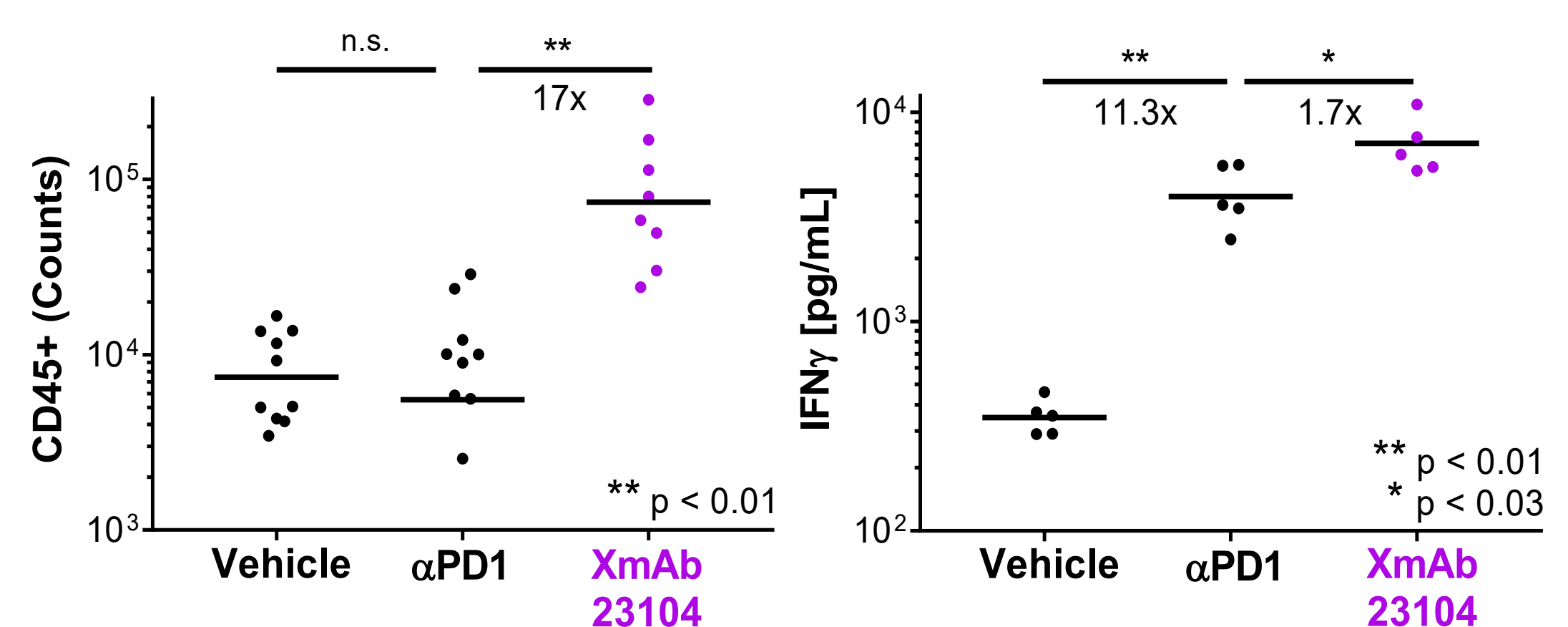
PD1 x ICOS bispecific antibodies were identified in empirical screens for synergistic activities

Multiple Healthy Donor SEB-stimulated human PBMC



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

