# Dual Blockade of PD1 and CTLA4 with Bispecific Antibody XmAb20717 Promotes Human T Cell Activation and Proliferation

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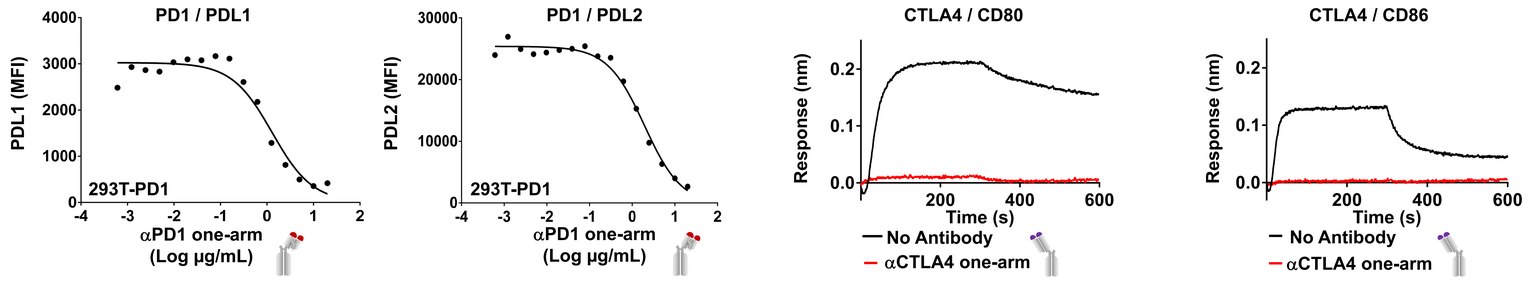
## Introduction

- Tumor-infiltrating lymphocytes (TILs) co-express multiple checkpoint receptors (Gros et al JCI 2014)
- TILs that co-express multiple checkpoint receptors may be resistant to single checkpoint blockade (Matsuzaki et al PNAS 2010, Fourcade et al Cancer Res 2012)
- Treatment of advanced melanoma patients with nivolumab plus ipilimumab significantly increases overall survival compared to ipilimumab or nivolumab alone (Wolchok et al. NEJM 2017)
- Targeting of PD1⁺CTLA4⁺ TILs with XmAb20717 may reproduce the efficacy of the combination regimen of nivolumab and ipilimumab therapy with reduced treatment-associated toxicities

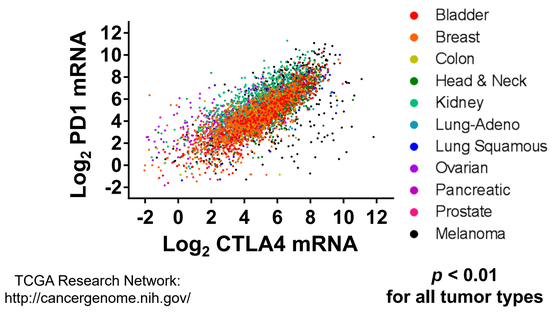
## Summary


- Dual blockade of PD1 and CTLA4 with XmAb20717 promotes superior T cell activation and proliferation compared to anti-PD1 alone
- Xmab20717 enhances allogeneic anti-tumor responses in mice
- XmAb20717 is currently under preclinical development with an expected IND filing in 2018


## XmAb20717 antibody domains block checkpoint receptor / ligand interactions




## TILs co-express PD1 and CTLA4

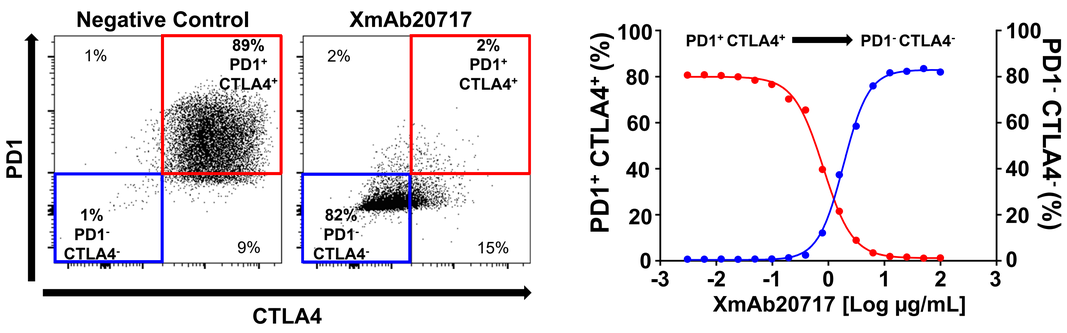



TCGA Research Network: http://cancergenome.nih.gov/

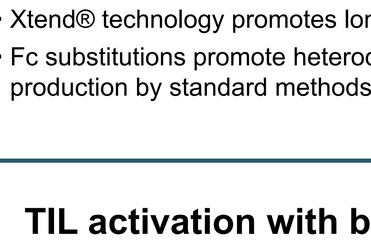
$p < 0.01$ for all tumor types

## XmAb20717 selectively occupies dual-positive cells

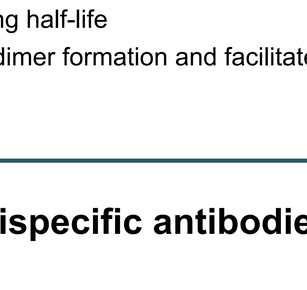
Receptor occupancy of 293T cells co-expressing PD1 and CTLA4




## XmAb20717 bispecific antibody design

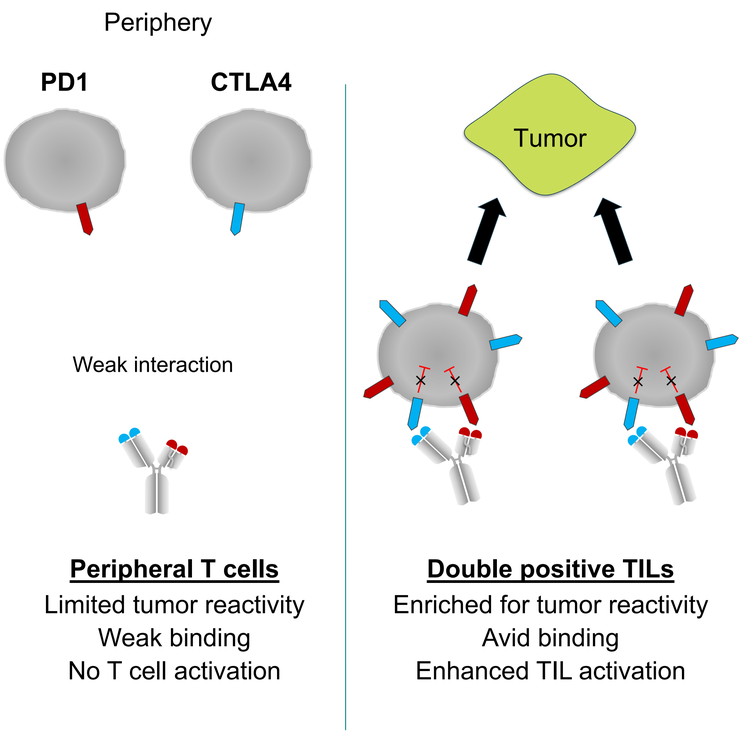



Purified XmAb20717
Size Exclusion Chromatograph



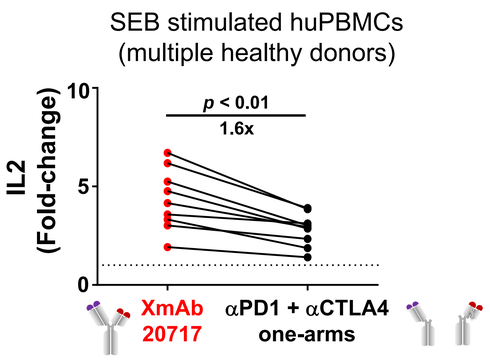

- Modified Fc domain eliminates FcγR interactions
- Xtend® technology promotes long half-life
- Fc substitutions promote heterodimer formation and facilitate production by standard methods

## TIL activation with bispecific antibodies

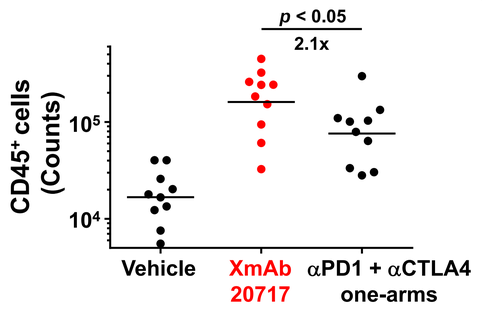


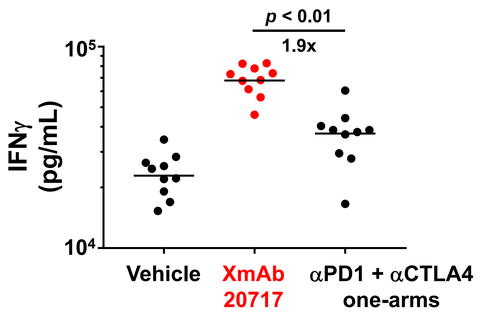

## Binding avidity of XmAb20717 contributes to T cell activation

SEB stimulated huPBMCs (multiple healthy donors)



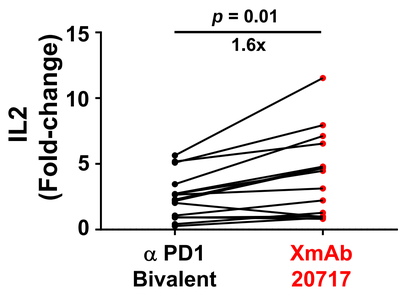

NSG mice engrafted with huPBMCs



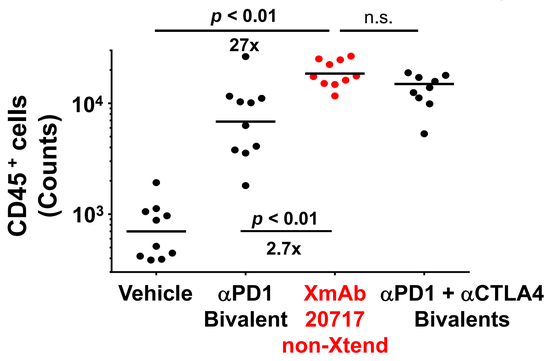



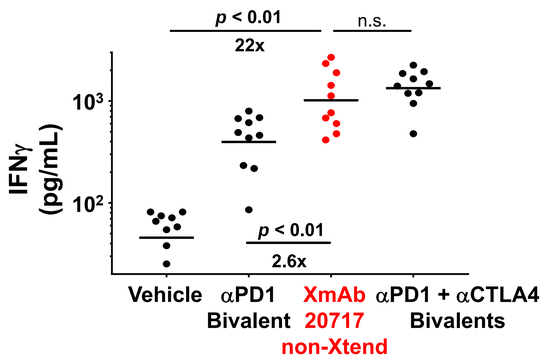

## XmAb20717 promotes superior T cell activation compared to an anti-PD1 bivalent antibody

SEB stimulated huPBMCs (multiple healthy donors)



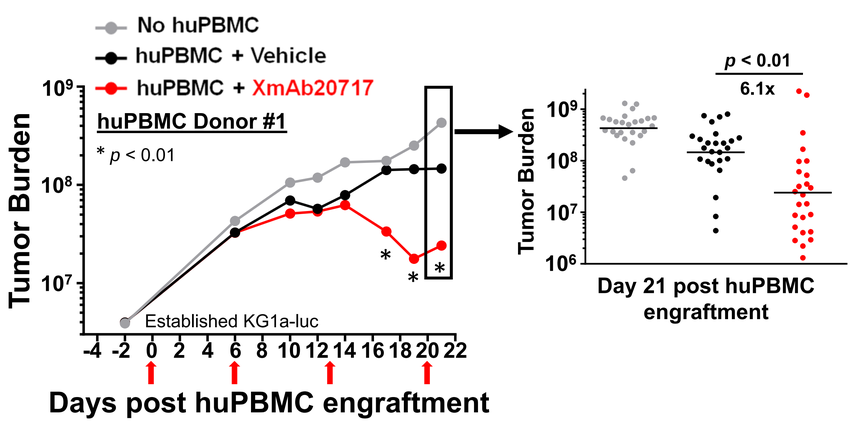

NSG mice engrafted with huPBMCs




## XmAb20717 enhances allogeneic anti-tumor responses in mice

NSG mice engrafted with KG1a-luc followed by engraftment with huPBMCs




Tumor burden presented is derived from the geometric mean flux acquired by IVIS imaging of KG1a-luc

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