Introduction

- Tumor infiltrating lymphocytes (TILs) co-express multiple checkpoint receptors in contrast to lymphocytes found in the periphery.
- TILs that co-express multiple checkpoint receptors may be resistant to single checkpoint blockade (Matsuzaki et al PNAS 2010, Fournade et al Cancer Res 2012, Gros et al JCI 2014).
- Treatment of advanced melanoma patients with nivolumab plus ipilimumab significantly increases progression-free survival compared to each monotherapy alone.
- Targeting of PD-1*CTLA-4* TILs with a bispecific antibody may reproduce the efficacy of the combination of nivolumab and ipilimumab therapy with reduced treatment-associated toxicities.

Summary

- Dual blockade of PD-1 and CTLA-4 promotes superior T cell activation, proliferation and T cell mediated anti-tumor efficacy compared to anti-PD-1 alone.
- XmAb20717 is a PD-1 x CTLA-4 bispecific antibody currently under pre-clinical development at Xencor.

Dual-checkpoint bispecific antibody design

- Modified Fc domain eliminates FcR interactions.
- Modified Fc domain with Xtend technology to promote long half-life.
- Fc substitutions promote heterodimer formation and facilitate purification by standard methods.
- Optimized Anti-PD-1 and CTLA-4 antibodies were plugged into the platform without further reformatting.

TIL activation with bispecific antibodies

Periphery

- Weak bispecific-antibody interactions
- No T cell activation

Tumor Microenvironment

- Dual-checkpoint positive TILs
- Avid bispecific antibody binding
- TIL activation

Component antibody domains block checkpoint receptor / ligand interactions

TILs co-express PD-1 and CTLA-4

- Bladder
- Breast
- Colon
- Head & Neck
- Kidney
- Lung Adeno
- Lung Squamous
- Ovarian
- Pancreatic
- Prostate
- Melanoma

PD-1 x CTLA-4 bispecific antibodies promote T cell activation in vitro

- SEB-stimulated lymphocytes
- Multiple healthy donors

IL-2 (Fold change)

- α PD-1 Bivalent
- α PD-1 x CTLA-4

- α CTLA-4 Bivalent
- α CTLA-4 x PD-1

** p ≤ 0.01
* p ≤ 0.05

PD-1 x CTLA-4 bispecific antibodies promote human T cell proliferation in vivo

- Study #1
- Study #2

PD-1 x CTLA-4 bispecific antibodies promote in vivo T cell mediated anti-tumor efficacy

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