Combination of PD1 blockade and T cell costimulation by bispecific antibodies promotes human T cell activation and proliferation

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Introduction

- Tumor infiltrating lymphocytes (TILs) express multiple check point receptors, in contrast to lymphocytes found in the periphery (Matsuzaki et al PNAS 2010, Fourcade et al Cancer Res 2012, Gros et al JCI 2014). TILs that co-express multiple check point receptors may be resistant to single-checkpoint blockade.
- We sought to identify an additional therapeutic modality to stack with checkpoint blockade that could increase patient response rate.
- The PD1+ TIL population is likely enriched for tumor-reactivity (Gros et al JCI 2014).
- Engagement of T cell costimulatory receptors with PD1 blockade could further increase T cell activation and proliferation of tumor-reactive TILs.
- We engineered a highly active anti-PD1 + anti-Costim bispecific antibody and characterized its T cell activation activity in vitro and in vivo.

Potential immunoregulatory T cell targets

PD1 x Costim bispecific:
- Double-positive cells are selectively occupied by PD1 + Costim bispecific
- IL2 production by SEB-stimulated human PBMCs is significantly increased by PD1 + Costim bispecific versus control (** p ≤ 0.01)
- Bispecific does not activate naïve cells
- Bispecific enhances T cell activation more than anti-PD1/CD80/CD86 antibody alone
- Bispecific enhances T cell activation more than combination of bivalent antibodies

Summary

- Anti-PD1 + anti-Costim bispecific antibody:
  - Is humanized and includes optimized component antibodies with high thermal stability
  - Contains a modified Fc domain with Xtend technology for long serum half-life
  - Selectively targets double-positive T cells
  - Enhances T cell activation in vitro and in vivo
  - Is well tolerated in cynomolgous monkeys with antibody-like pharmacokinetics
  - Is efficiently manufactured using standard antibody production methods.

These results support clinical testing of an anti-PD1 + anti-Costim bispecific in cancer.