**Introduction**

- Tumor infiltrating lymphocytes (TILs) often express multiple immune checkpoints and costimulatory receptors (Matsuzaki et al PNAS 2010, Fourcade et al Cancer Res 2012, Gros et al JCI 2014).
- 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 together with PD1 blockade could further increase activation and proliferation of tumor-reactive TILs.
- Activity screens for multiple PD1/costimulatory combinations demonstrated compelling activity for a PD1 and ICOS pairing.
- We engineered XmAb23104, a highly active anti-PD1 × anti-ICOS bispecific antibody, and characterized its T cell activation activity in vitro and in vivo.

**PD1 × ICOS pairing enhances T cell activation in vitro**

- IL2 production is significantly increased by XmAb23104 versus bivalent antibodies
- Receptor occupancy of PD1 and ICOS on human CD3+ T cells stimulated with SEB

**XmAb23104 significantly enhances T cell activation in vitro**

- Selective TIL activation with bispecific antibodies

**XmAb23104 exhibits a multi-gene expression signature consistent with ICOS costimulation**

- SEB-stimulated human PBMCs (multiple healthy donors)

**Summary**

- XmAb23104 anti-PD1 × anti-ICOS bispecific antibody:
  - Is humanized and includes optimized component antibodies
  - Contains a modified Fc domain with Xtend technology for long serum half-life
  - Selectively targets double-positive T cells
  - Enhances T cell activation more than anti-PD1 or anti-ICOS antibodies
  - Is well tolerated in cynomolgus monkeys with antibody-like pharmacokinetics
  - Is efficiently manufactured using standard production methods
  - XmAb23104 is currently under preclinical development with an expected IND filing in 2018.