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Combining CD27 costimulation and PD-1 blockade into a bispecific antibody improves T cell activation and anti-tumor activity over combination of individual antibodies

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CSO

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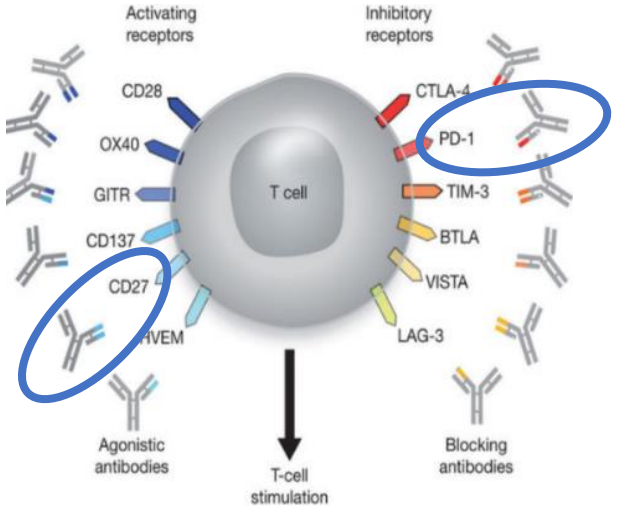
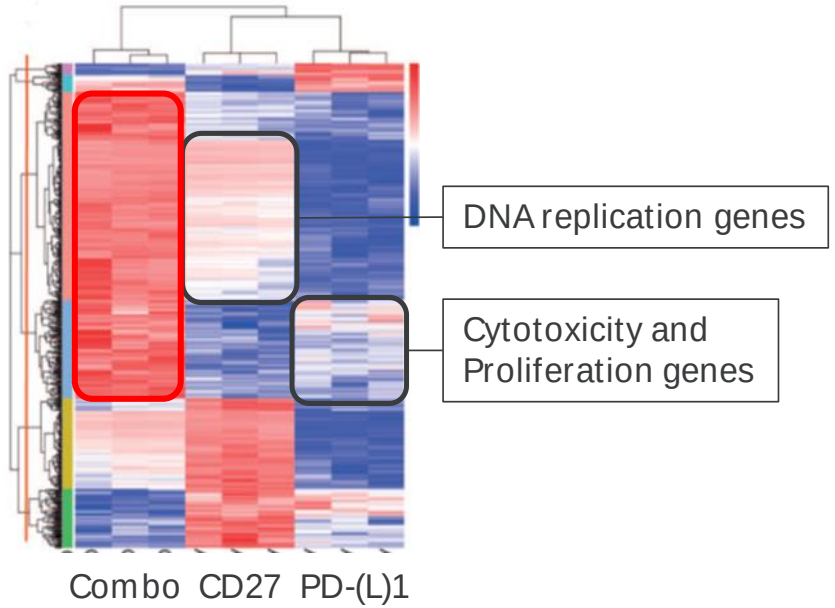
Disclosure: I am employed by Celldex and own stock in Celldex

Rationale for Combination of CD27 Costimulation with PD-(L)1 Blockade

CD27 and PD-1 are complementary pathways for T cell activation- CD27 activation and PD-1/L1 blockade cooperate to drive proliferative and cytotoxic gene expression programs in CD8+ T cells



From Chen and Mellman, Immunity 2013

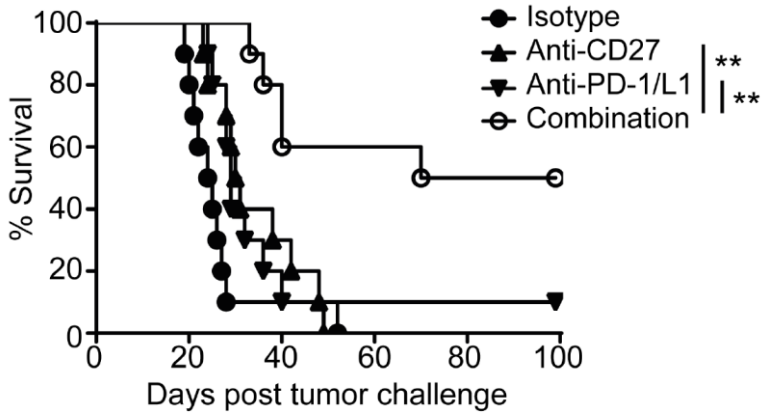


Gene expression in Pmel-Tg CD8+ T cells stimulated in vivo with peptide and Abs

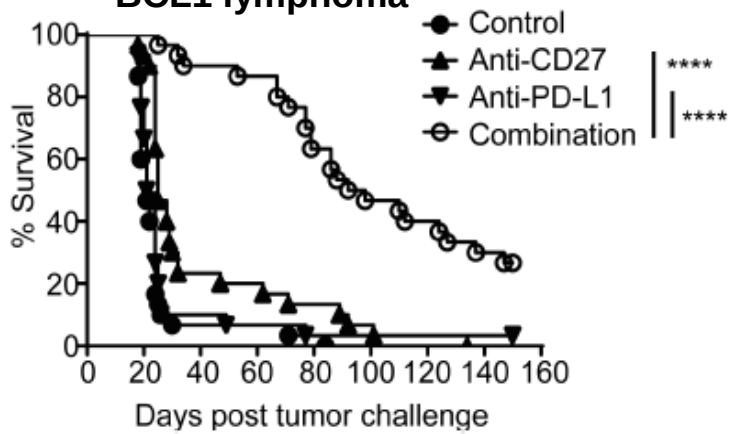
Buchan et al. Clin Cancer Res. 2018

CD27 mAb is synergistic with PD-1/L1 blockade in tumor models

Pmel adoptive T cell therapy



BCL1 lymphoma

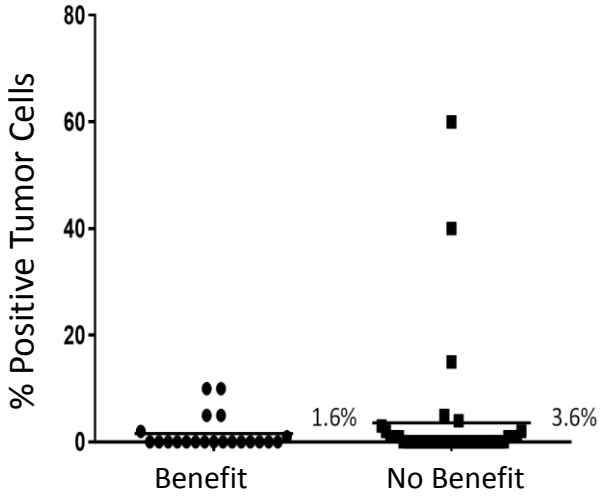


Clinical Experience with Varlilumab (CD27 agonist mAb) and Nivolumab Supports BsAb Approach

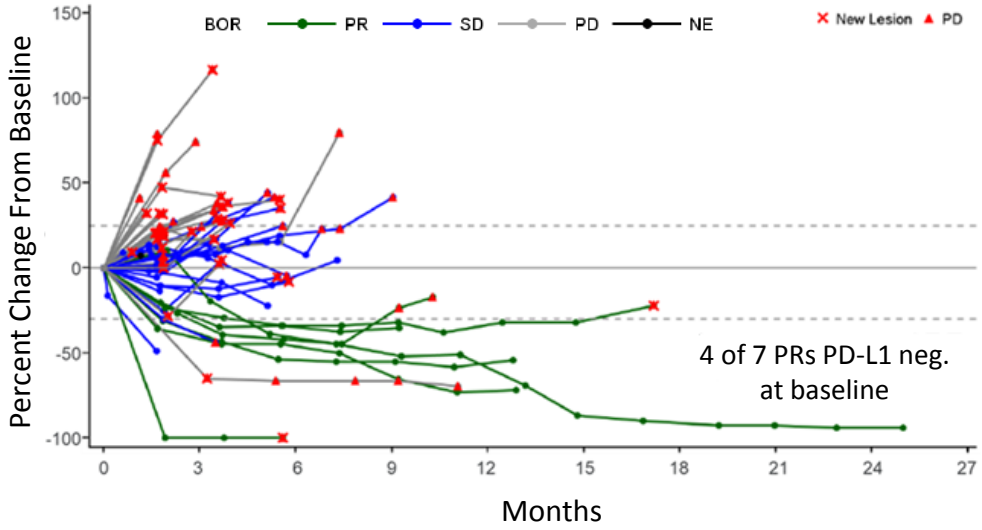
- Combination therapy was generally well tolerated across indications at all varlilumab dose levels/schedules tested
- Durable responses observed in patients with “cold” tumors with low expectation of response to CPI monotherapy

Most experience in ovarian cancer cohort (response evaluable n=54 ORR 13%)

Low PD-L1 Expression at baseline



Durable Responses



Higher doses of varlilumab (3 mg/kg Q2W) trended towards better clinical activity than lower/less frequent dosing

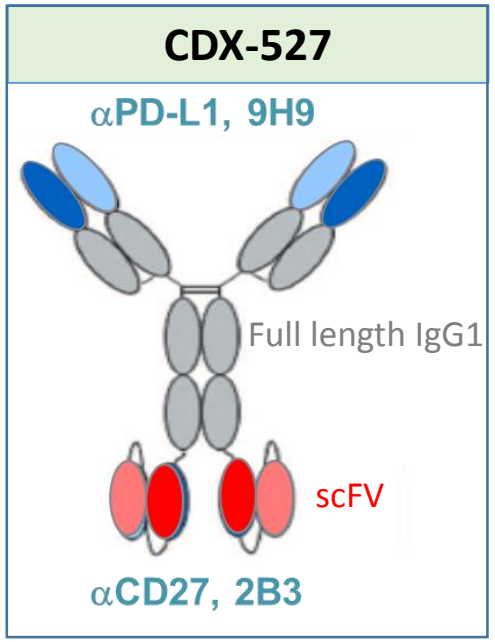
- Supports combining CD27 agonist and PD-1 blockade at fixed dose and schedule

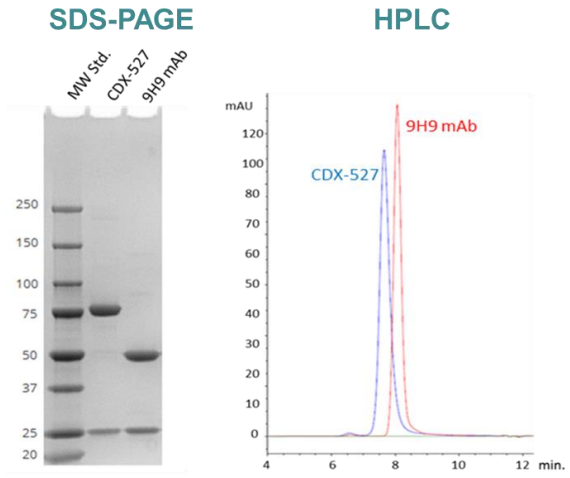
CDX-527: α-PD-L1 x α-CD27 BsAb

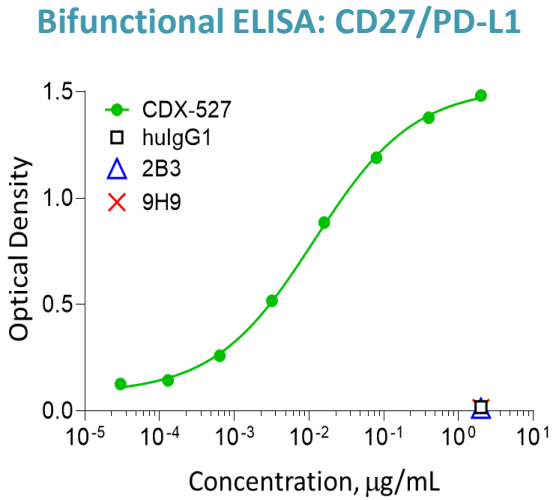
Novel PD-L1 and CD27 mAbs were developed using human Ig transgenic mice
Selected 2B3 (CD27) and 9H9 (PD-L1) for BsAb based on activity and manufacturability

IgG-scFv format

- Include human Fc region as part of the BsAb construct
  - Retain Fc receptor cross-linking capability
  - Retain FcRn binding activity for PK
  - Standard purification methods
- Significant experience with IgG-scFv format including late phase trials
- Tetravalent
  - Bivalent for CD27
  - Bivalent for PD-L1





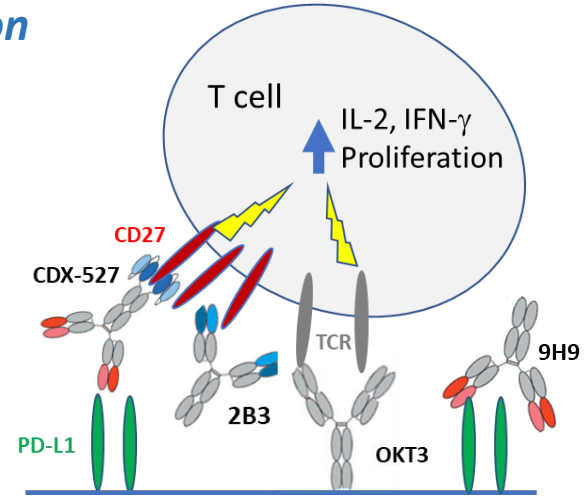


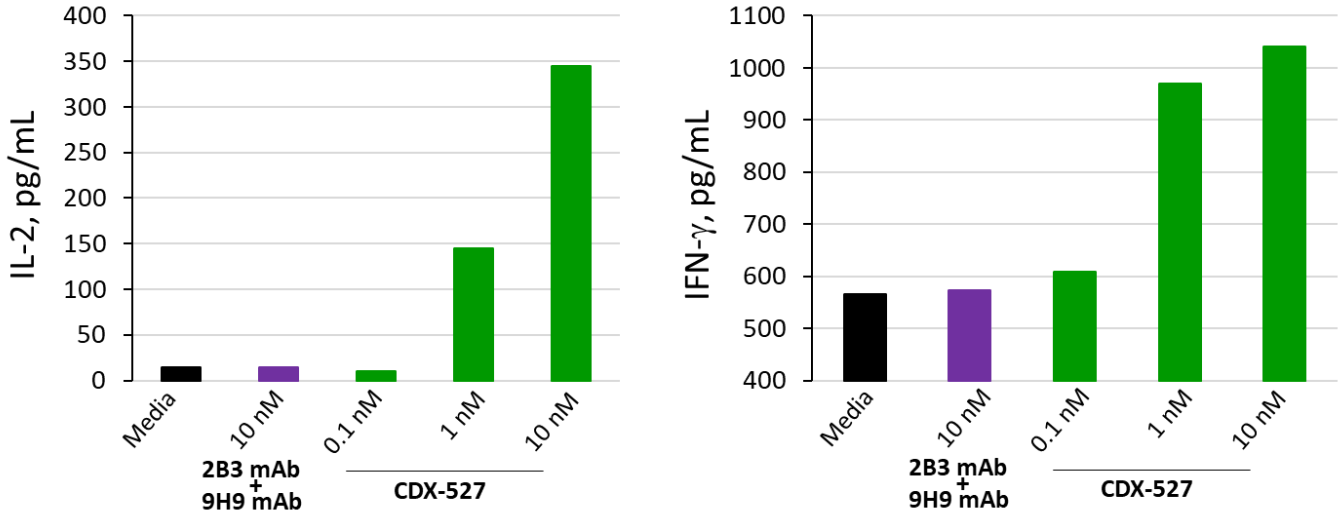
CD27 costimulation can occur through both FcR and/or PD-L1 cross-linking

CDX-527: Greater T cell Activation Than Combination of Parental mAbs

T cell costimulation

Simultaneous CD27 and TCR stimulation activates T cells

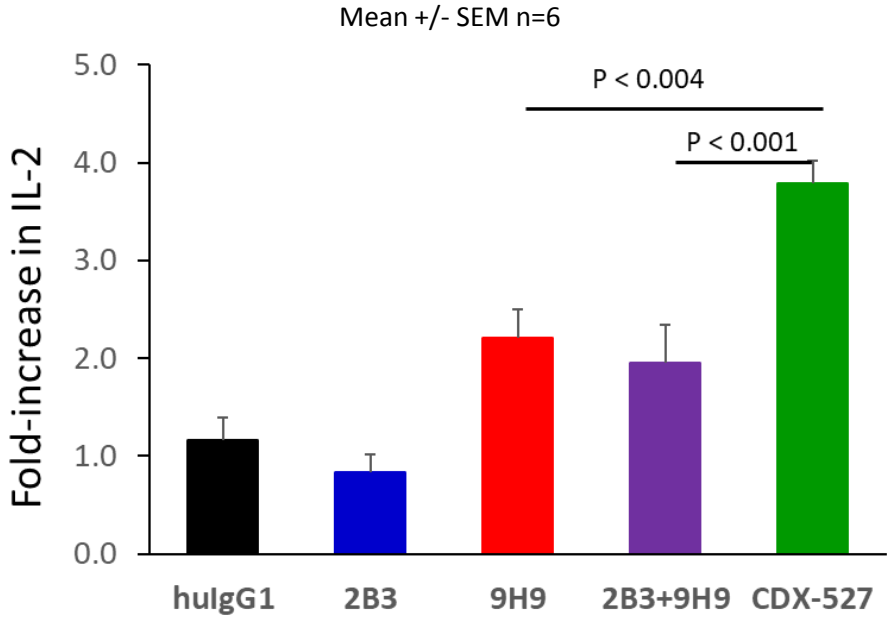




Representative donor

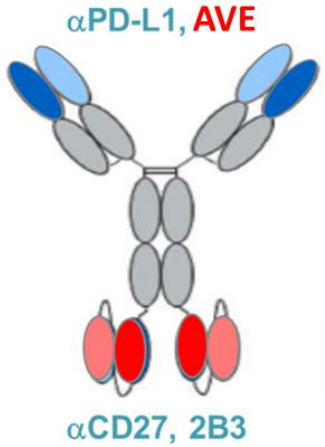
Mixed lymphocyte reaction

T cell activation is enhanced with PD-1 blockade and CD27 costimulation

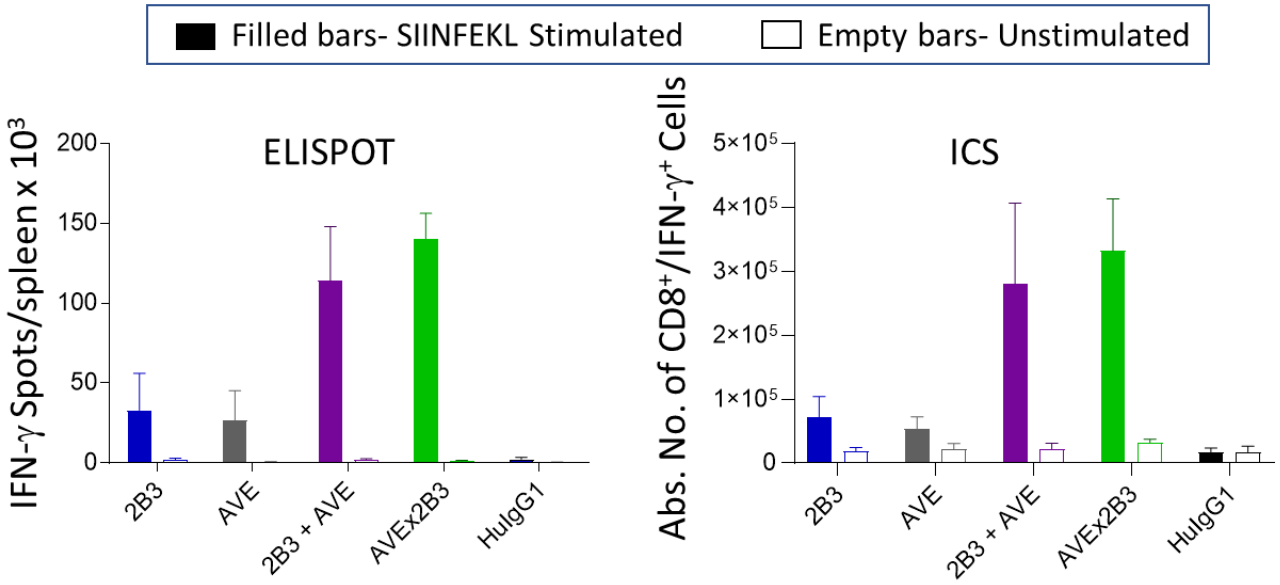


Surrogate BsAb for in vivo Studies

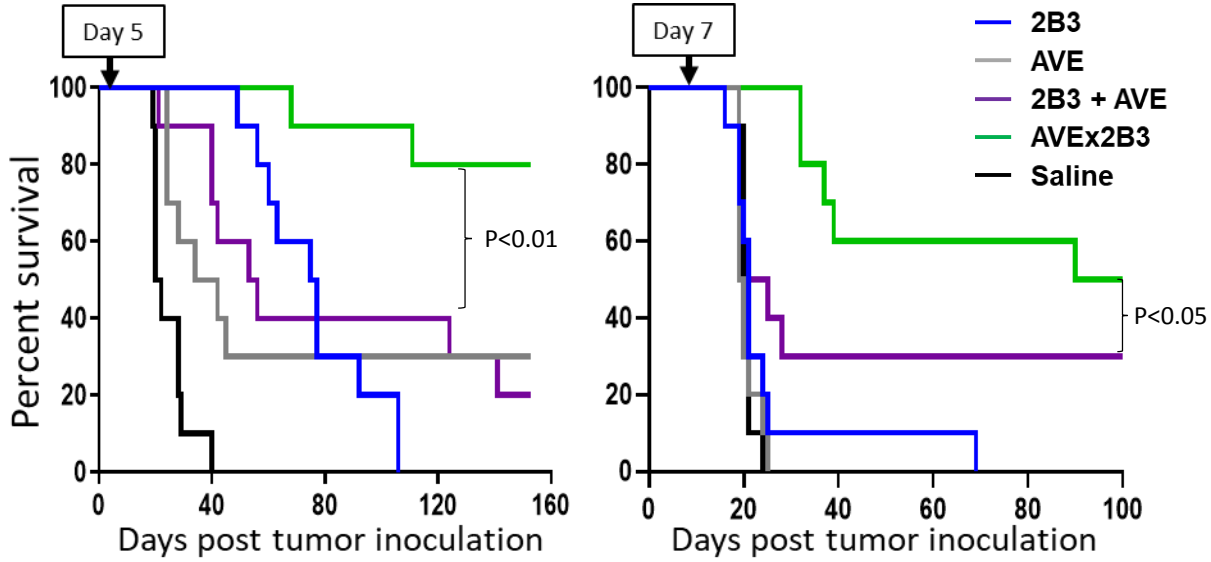
- Anti-PD-L1 mAb 9H9 binds macaque PD-L1, but does not cross react with rodent PD-L1
  - Substitute with avelumab (AVE), which binds equally well to human and mouse PD-L1
- Anti-CD27 mAb 2B3 binds macaque CD27, but does not cross react with rodent CD27
  - Utilize human CD27 transgenic mouse for in vivo studies
- Design and develop AVEx2B3 in same format as CDX-527
- AVEx2B3 showed binding and T cell activities similar to CDX-527



Activation of vaccine (OVA) CD8 T cell response



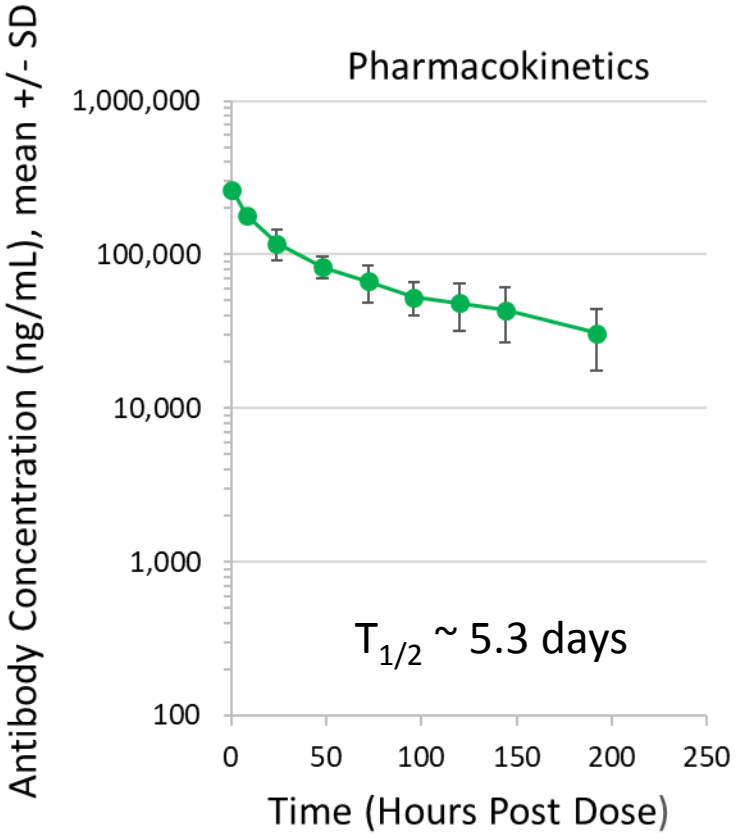
Anti-lymphoma activity (BCL-1)

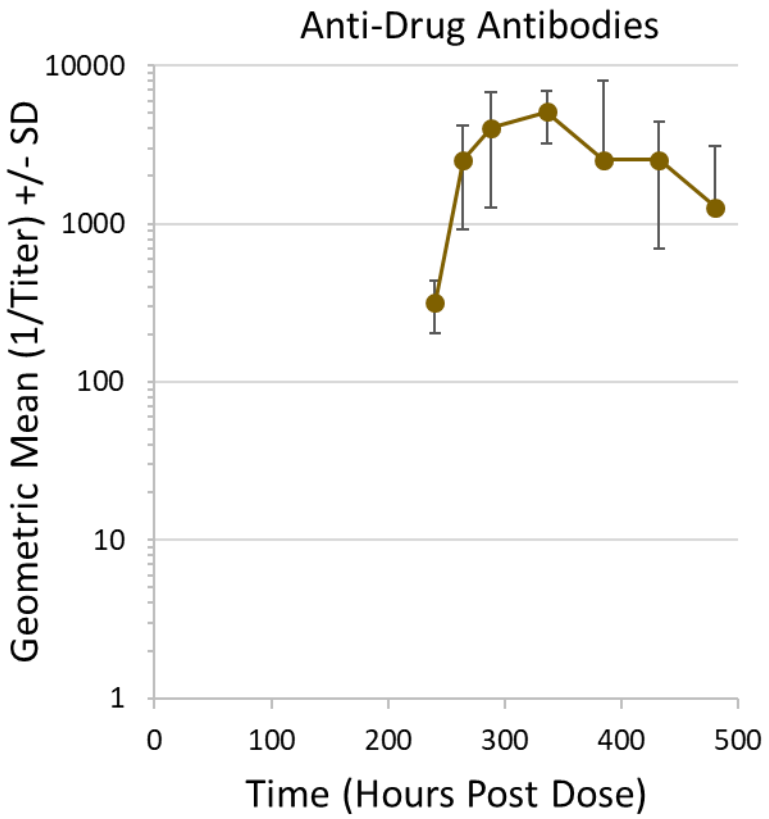


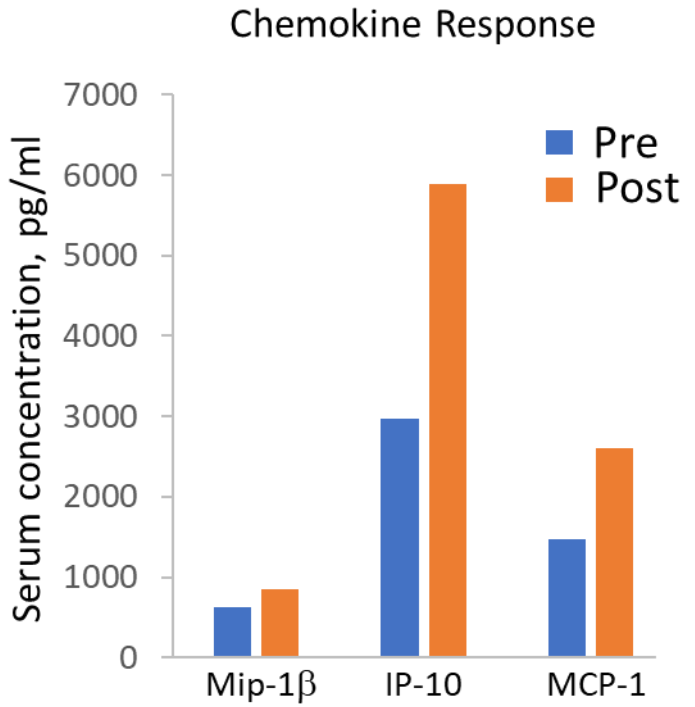
Pharmacokinetics and pharmacodynamics of CDX-527 in a pilot NHP study

21 day study in 3 cynomolgus macaques administered a bolus injection of 7 mg/kg CDX-527

- No significant changes observed in any clinical parameters
- PK similar to mAbs- Strong ADA response
- Upregulation of chemokine levels associated with CD27 activation







Summary and next steps

- Bispecific antibodies (BsAbs) that engage two independent pathways involved in controlling immune responses to tumors are a rapidly growing area for the development of next generation PD-1 inhibitors
  - Twenty unique PD-(L)1 based bispecific molecules in clinical development in 47 separate trials (*clinicaltrials.gov*)
- Our prior clinical experience with combining CD27 activation and PD-1 blockade provides the rationale for linking these two pathways into one molecule
- The preclinical studies demonstrate that CDX-527 is more potent at T cell activation and anti-tumor immunity than the combination of parental monoclonal antibodies
- Next steps for CDX-527 include:
  - Completion of CDX-527 GMP manufacturing activities
  - Completion of IND-enabling studies
  - IND planned for H1 2020
  - Phase 1 dose escalation trial

Acknowledgements

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