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& Convention Center



Society for Immunotherapy of Cancer

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2017

PD-1 Blockade: Understanding CD8 T Cell Rescue for Insights into Cancer Immunotherapy

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Society for Immunotherapy of Cancer

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Presenter Disclosure Information

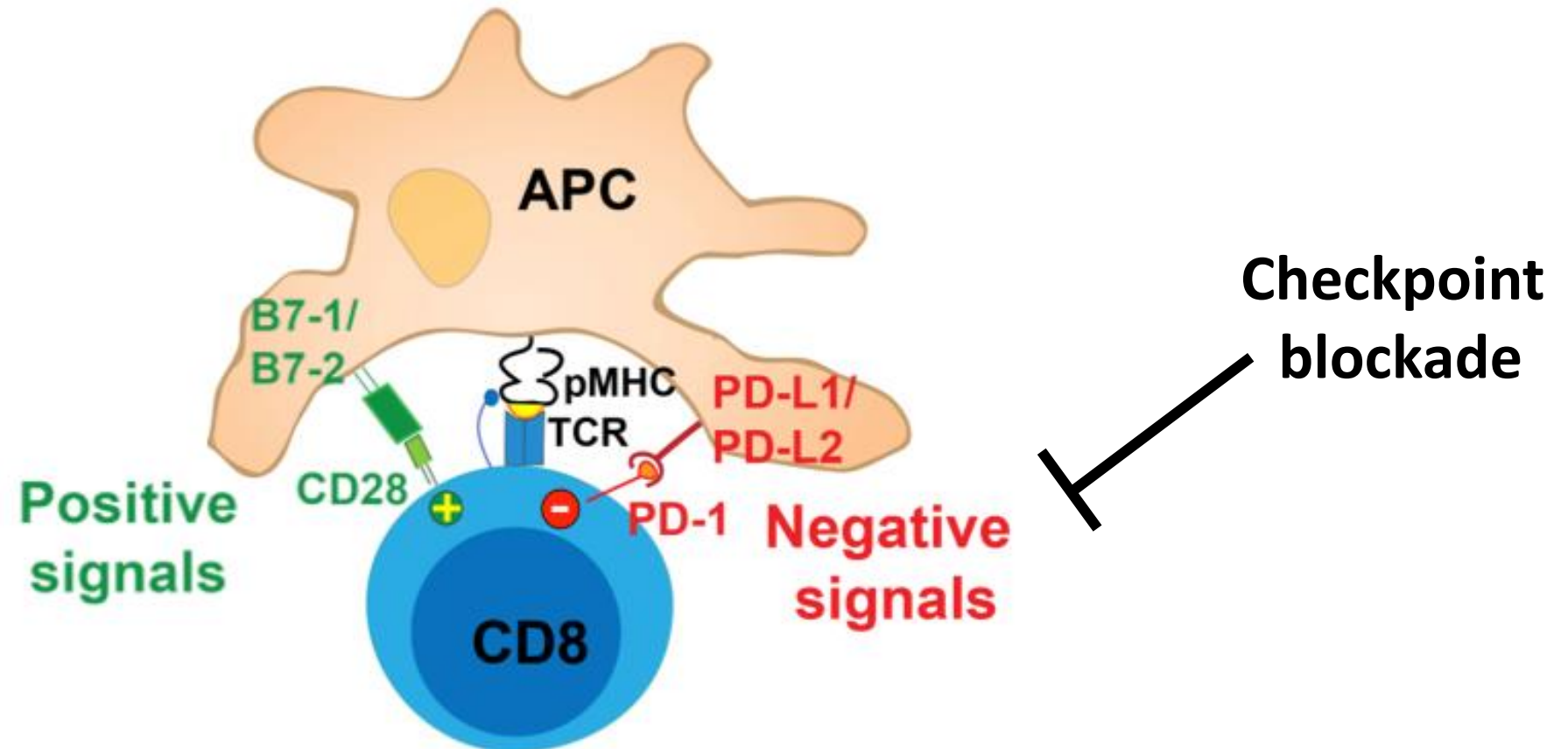
Alice O. Kamphorst

The following relationships exist related to this presentation:

Grant/research support from Merck.

There will not be discussion about the use of products for non-FDA approved indications in this presentation.

What are the requirements for T cell rescue?



Is CD28 co-stimulation required for rescue of exhausted CD8 T cells by PD-1 blockade?

Mouse model:

Lymphocytic choriomeningitis virus (LCMV) chronic infection.

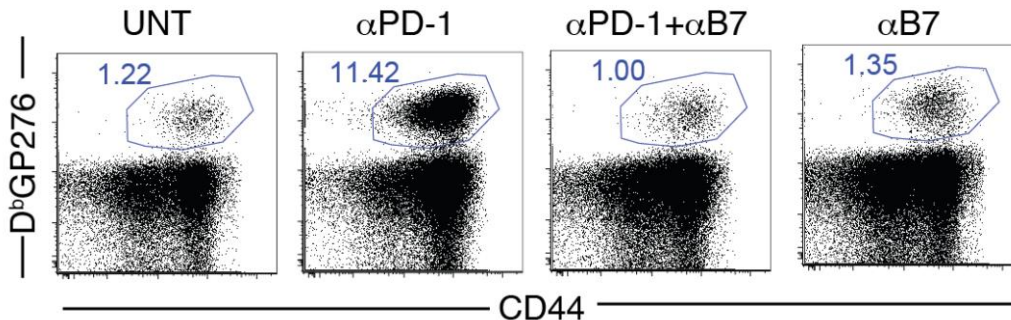
Experimental approaches:

- 1) Anti-B7-1 and anti-B7-2 blocking antibodies;**
- 2) CD28-deficient (CD28KO) CD8 T cells;**
- 3) CD28 conditional deletion on CD8 T cells.**

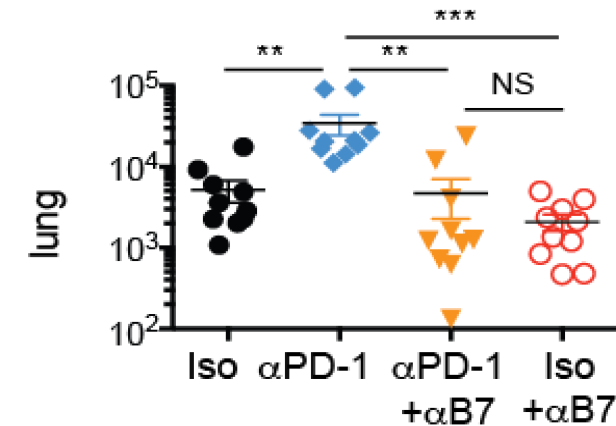
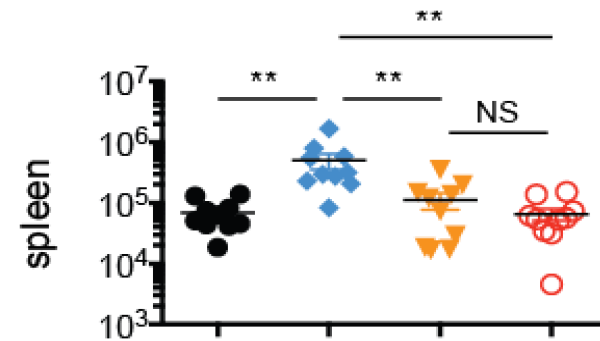
Blockade of B7 signals abrogates rescue of CD8 T cells by PD-1 therapy



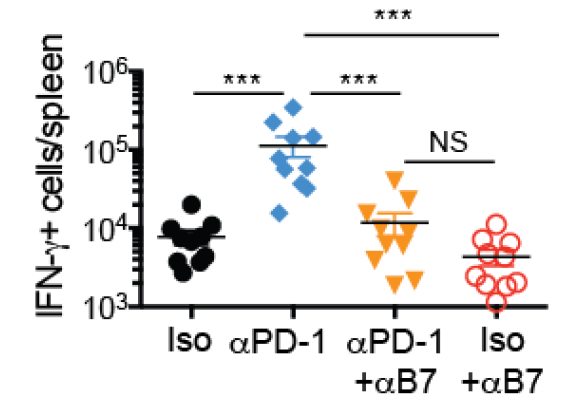
LCMV-GP276-specific CD8 T cells in spleen (%CD8)



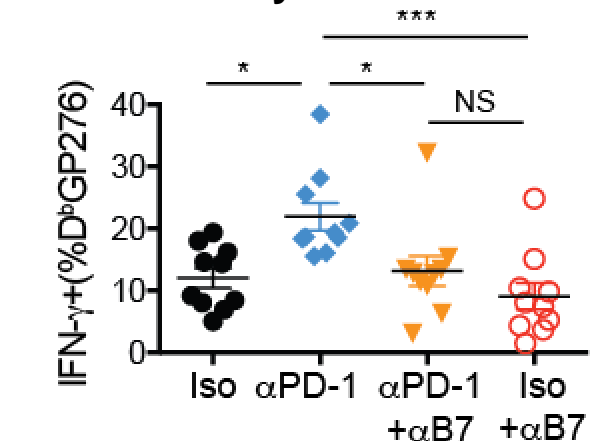
GP276-specific CD8 T cells numbers



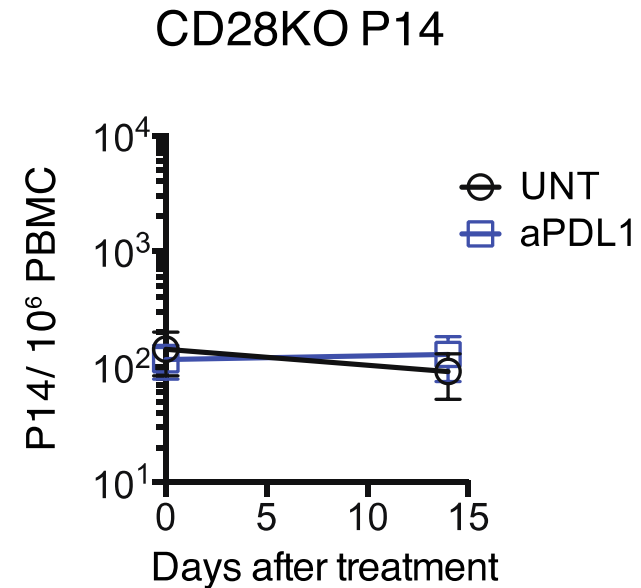
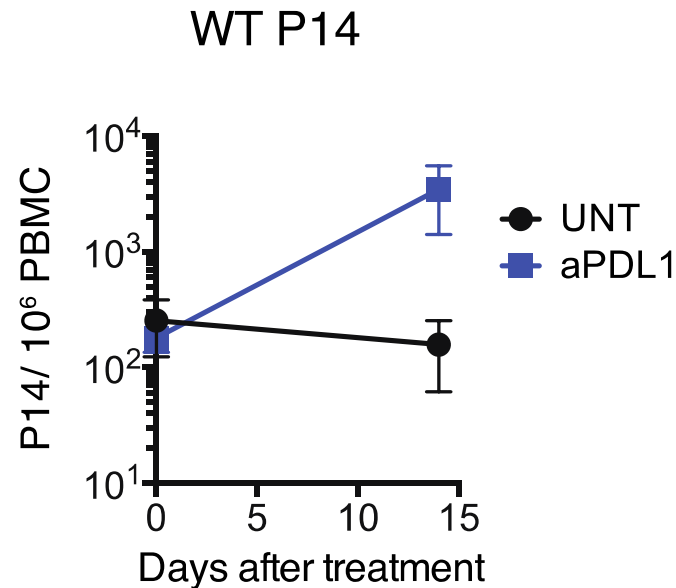
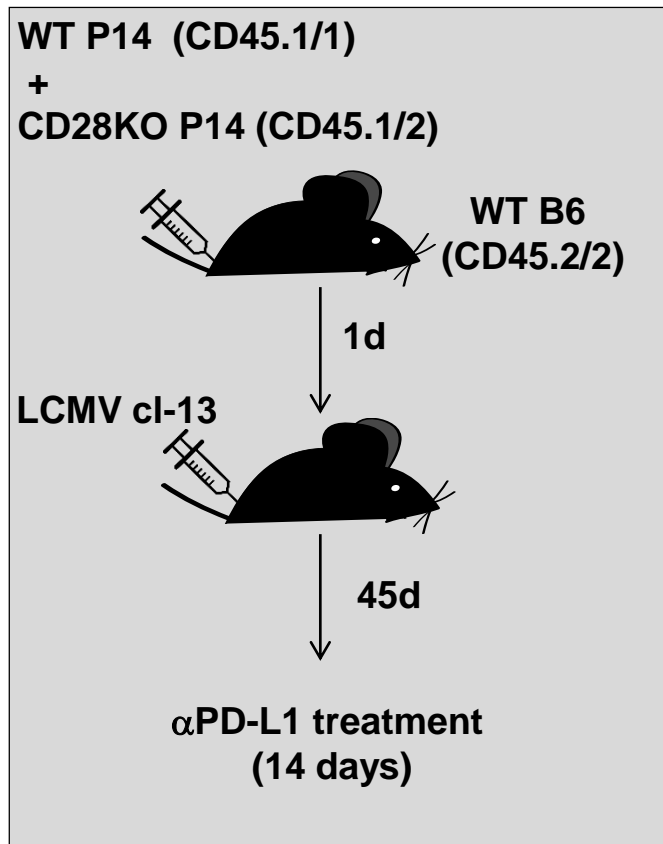
GP276-peptide stimulation



Functionality of GP276-CD8



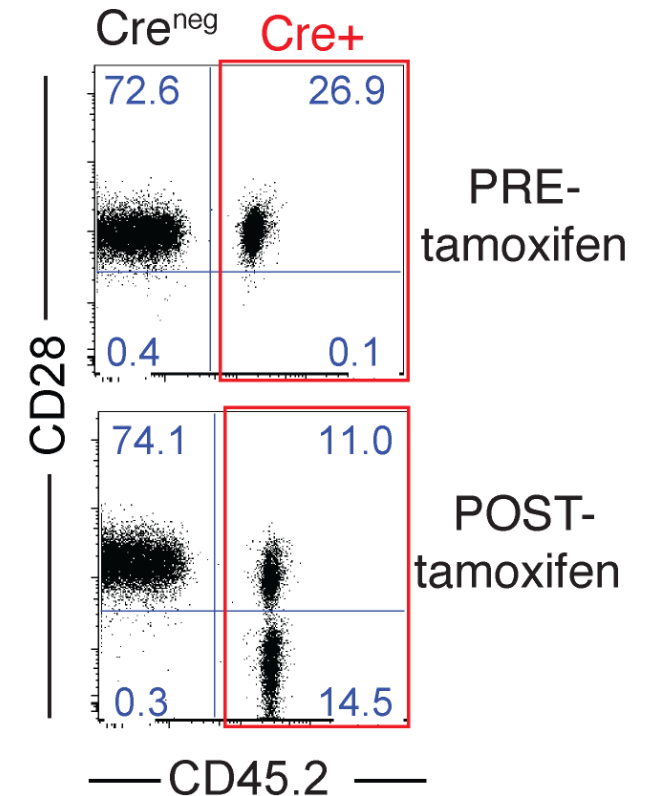
CD28-deficient CD8 T cells do not expand following blockade of the PD-1 pathway



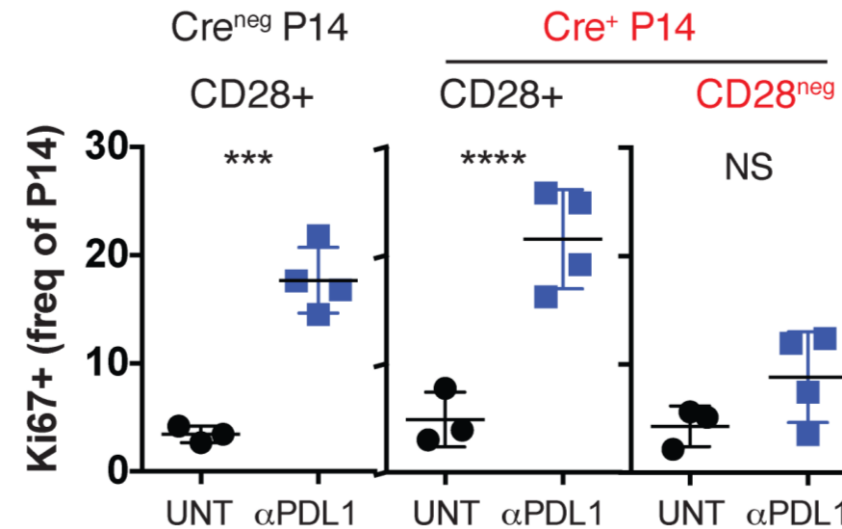
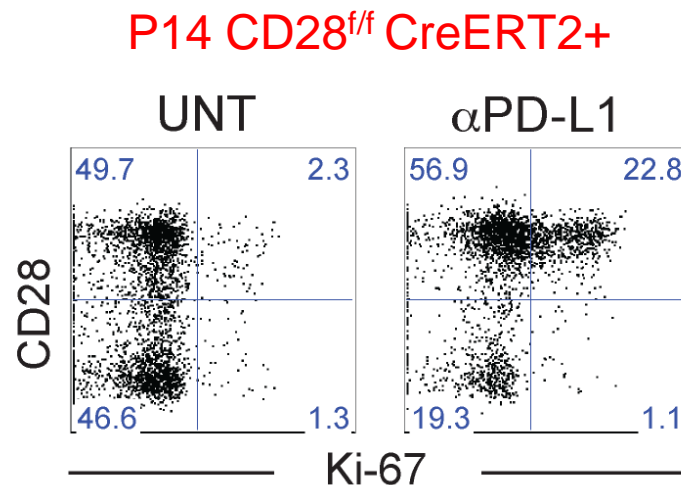
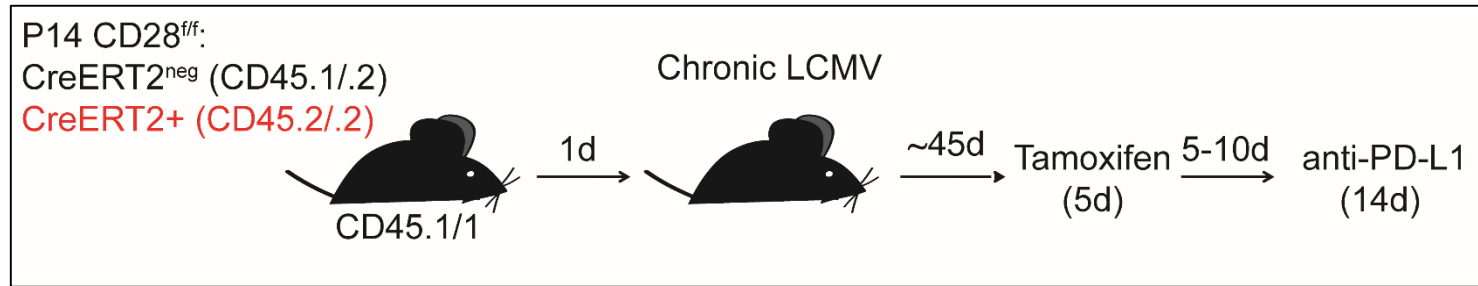
Conditional CD28 gene deletion by tamoxifen administration

- ✓ CD28^{flox/flox} mice: loxP sites flanking exons 2 and 3 of murine *Cd28*.
(Zhang, *J. Clin Invest* 2013)
- ✓ CD28^{flox/flox} mice crossed to Cre-ERT2 (ROSA26 locus).
- ✓ **Successful ubiquitous induction of Cre activity and CD28 gene deletion after tamoxifen administration.**

CD8 T cells



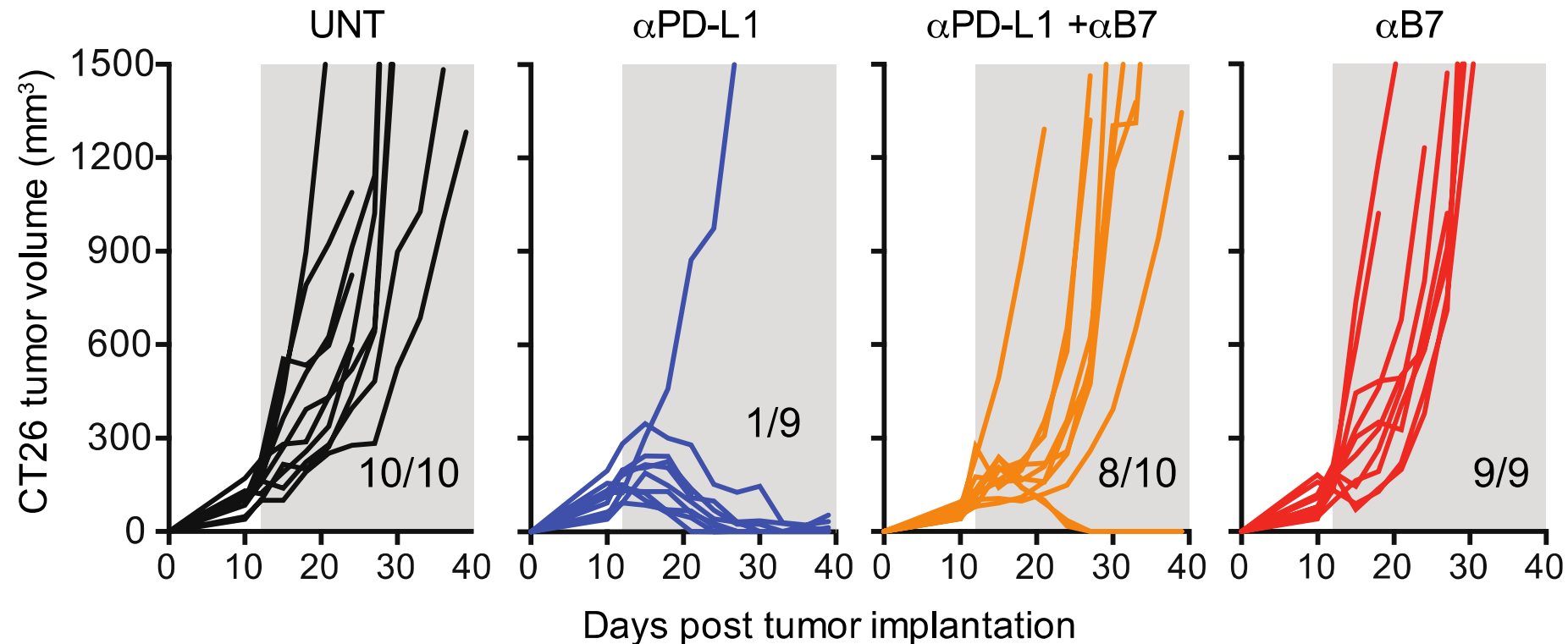
CD28^{neg} exhausted CD8 T cells fail to proliferate following PD-1 targeted therapies



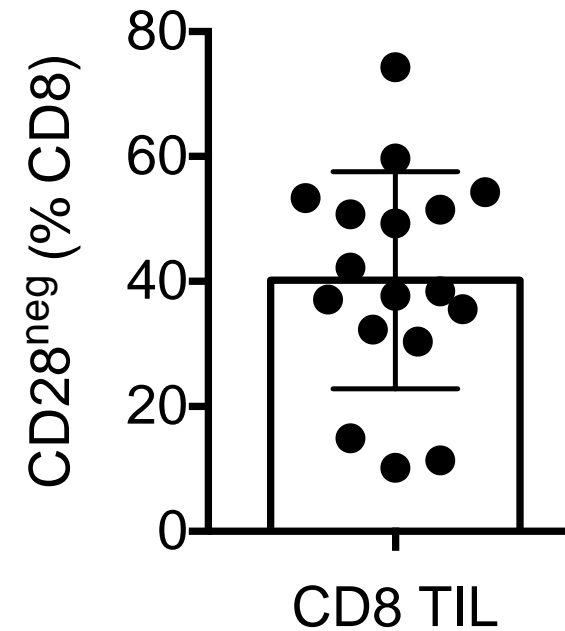
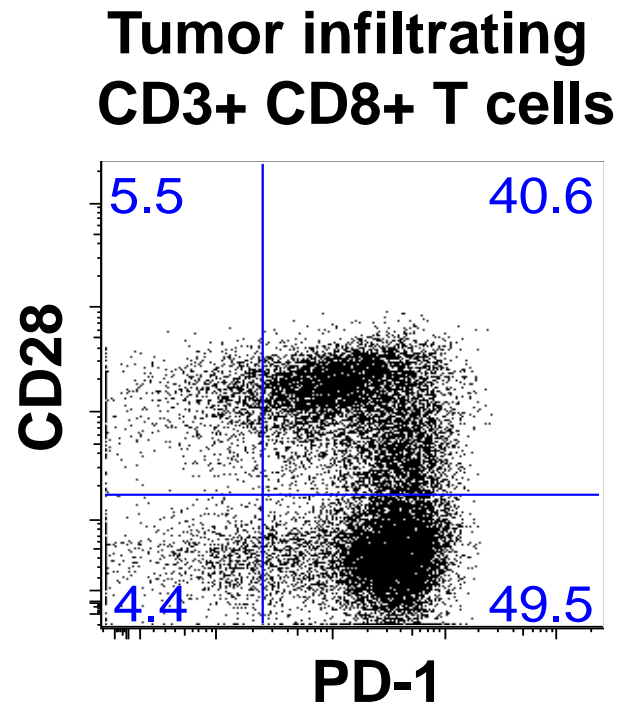
CONCLUSIONS I

- **Proliferation of exhausted CD8 T cells following blockade of the PD-1 pathway is CD28-dependent.**
- **Our findings imply that CD28 signaling on exhausted CD8 T cells would be essential for optimal PD-1 directed cancer immunotherapy.**

Effectiveness of PD-1 therapy in CT-26 tumors relies on the CD28/B7 pathway

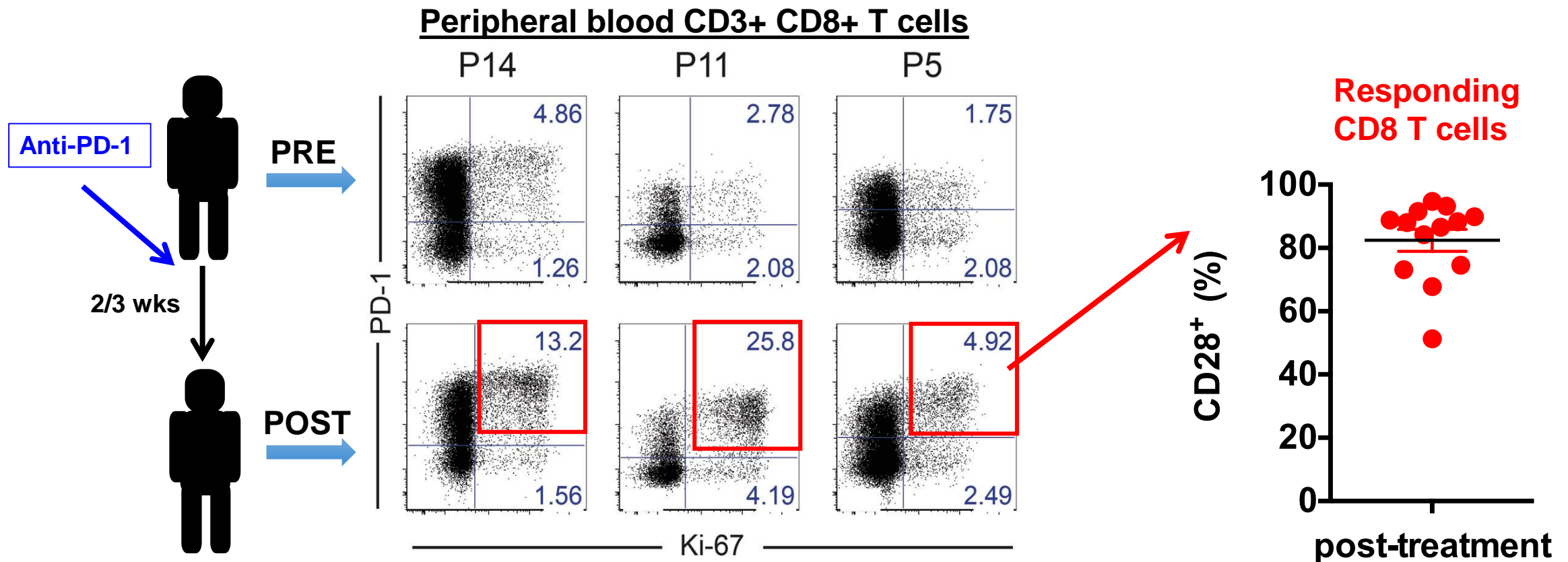


In human lung tumors (NSCLC) a large fraction of PD-1+ CD8 T cells are CD28^{neg}



NSCLC (non-small cell lung cancer)

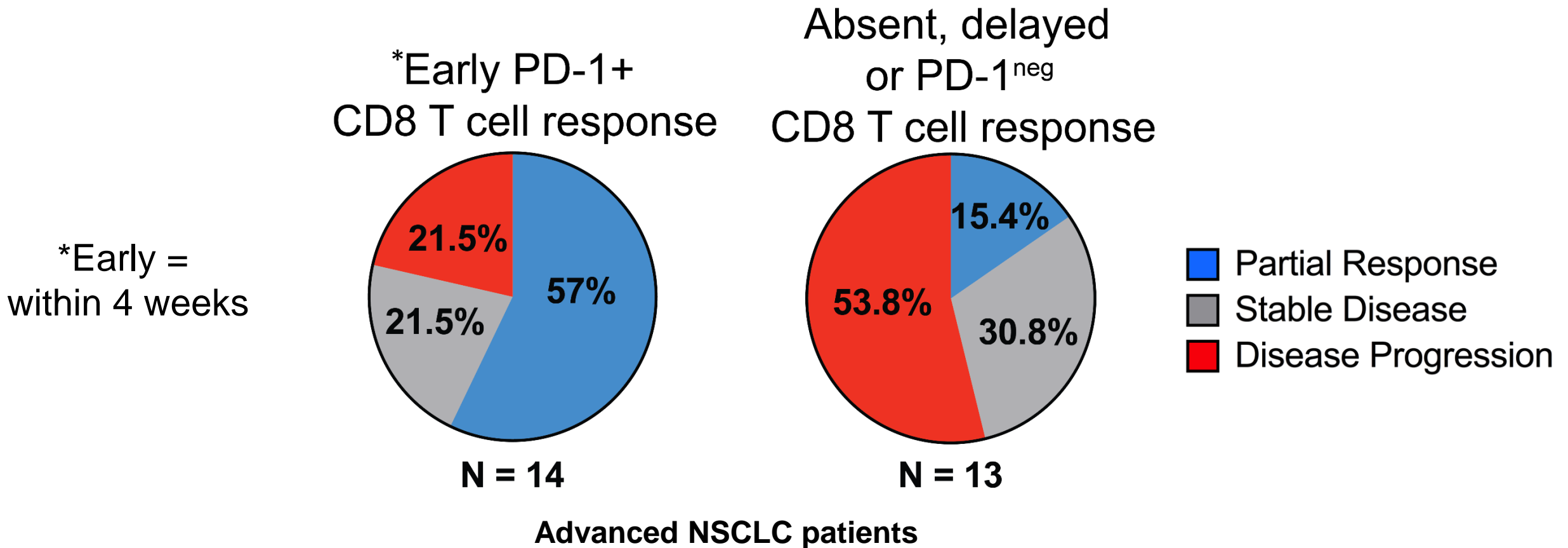
PD-1 targeted therapy on lung cancer patients induces proliferation of CD28⁺ PD-1⁺ CD8 T cells



FINAL CONCLUSIONS

- **Most CD8 T cells in peripheral blood responding to PD-1 blockade express CD28; but many CD8 T cells infiltrating human lung tumors are CD28^{neg} → Implies selective proliferation of CD28⁺ tumor-specific CD8 T cells during PD-1 therapy.**
- **CD28 expression on PD-1⁺ CD8 T cells and the presence of B7-expressing antigen presenting cells could be potential biomarkers for predicting efficacy of PD-1 directed immunotherapies.**
- **Positive signals (CD28) are necessary to reinvigorate exhausted CD8 T cells during checkpoint blockade therapy (PD-1).**

Immunological analysis in peripheral blood may help predict clinical outcome to PD-1 therapy



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