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WASHINGTON, D.C.
Walter E. Washington
Convention Center

sitc
Society for Immunotherapy of Cancer

A New Immunomodulatory Strategy of Inhibiting Glyco-immune Checkpoints Using *EAGLE* Technology

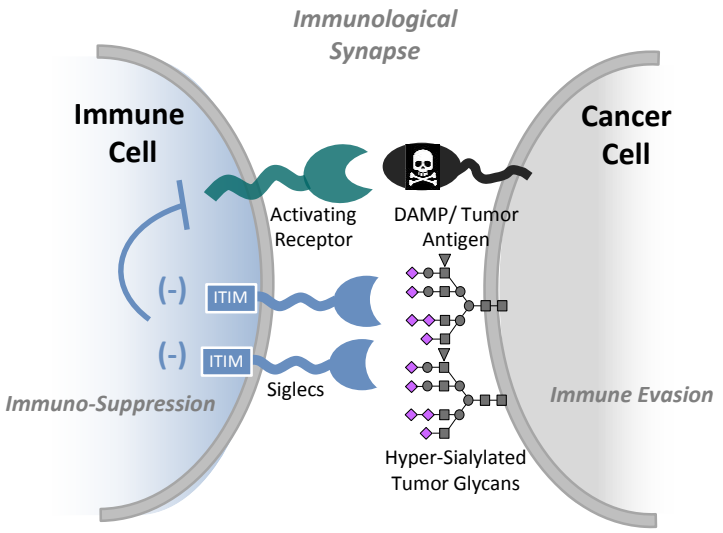
Li Peng

Presenter Disclosure Information

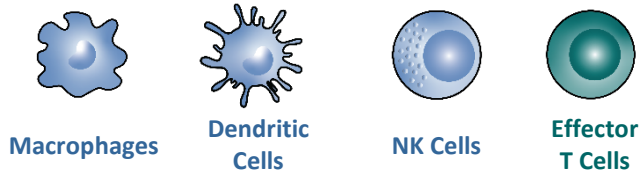
Palleon Pharmaceuticals, Employee

Glyco-Immune Checkpoints Suppress Multi-Facets of Cancer Immunity

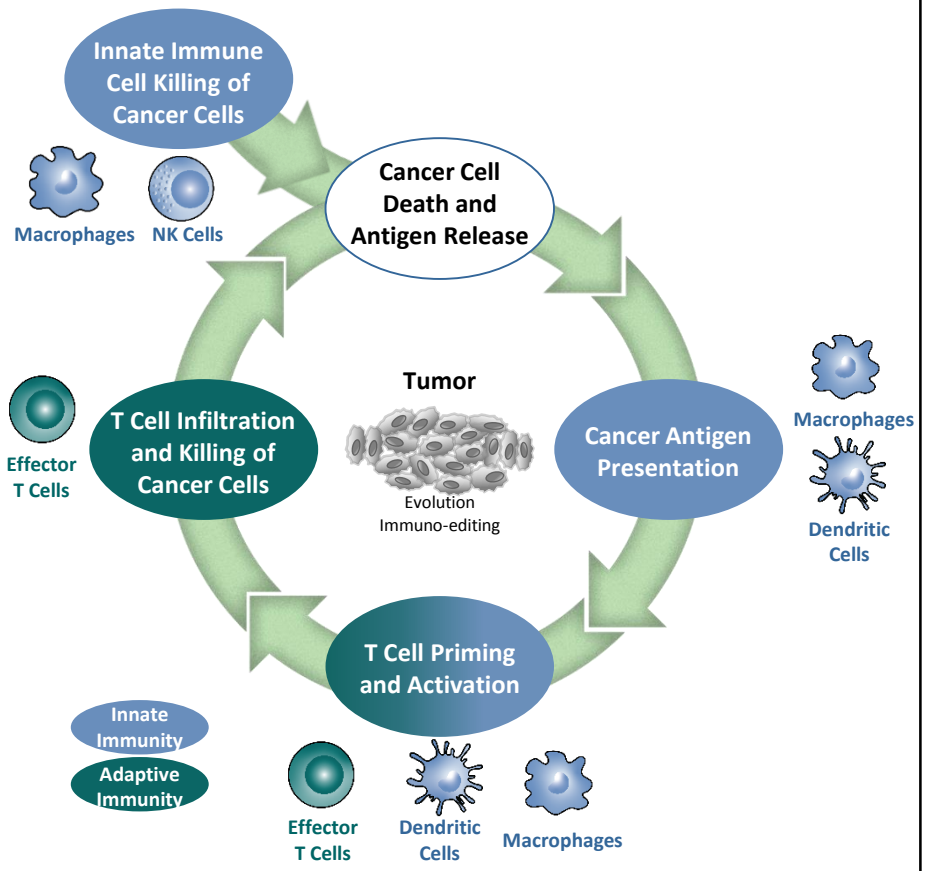
Glyco-Immune Checkpoints in Cancer:
The Siglec/Sialoglycan Axis



Siglec Binding to Hyper-Sialylated Tumor Glycans Blocks Innate & Adaptive Immune Cell Activation



Cancer Immunity Cycle
The Roles of Siglec/Sialoglycan Axis

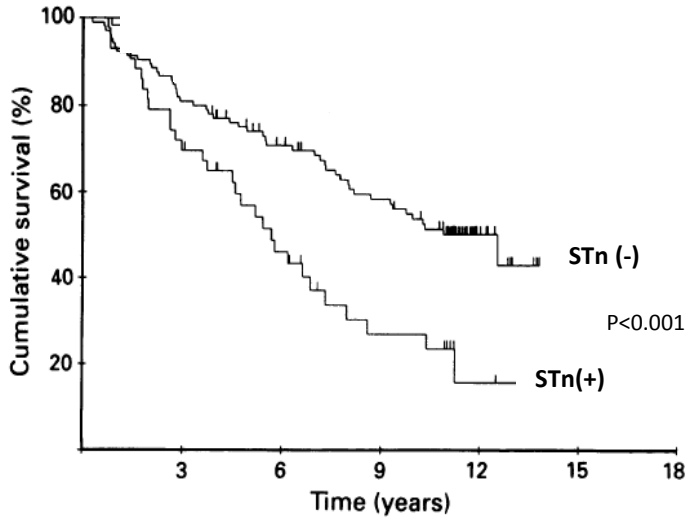


Adopted from Chen Daniel S. et al. Immunity

The Tumor Glyco-Code – New Insights into Prior Observations

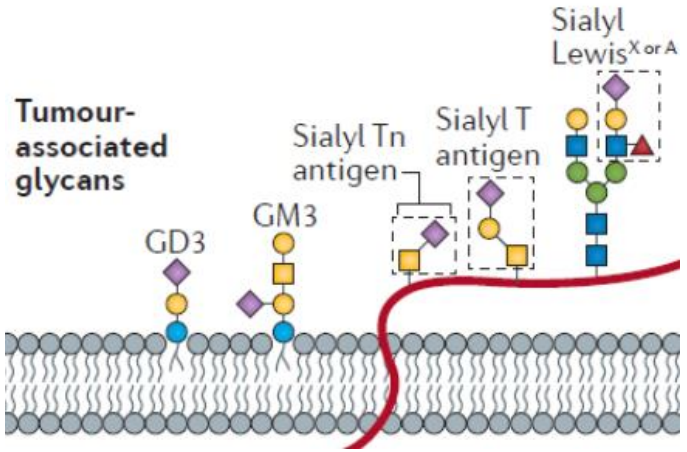
- Unique tumor surface glycans were first observed in the 1960's.
- Associations with poor outcome were established in the 1980's and 1990's.
- Hypersialylation is a common feature of tumor-specific glycans.

STn (Sialyl Thomsen-Nouvelle) in Node Positive Breast Cancer Survival: Tumor-Specific Glycan



Miles, 1994

Hypersialylation Coat of Cancer Cells



Adopted from Yvette van Kooyk, *Nature Reviews Immunology,* 2018

Development of the *EAGLE* Therapeutic Platform (Enzyme-Antibody Glycan-Ligand Editing)

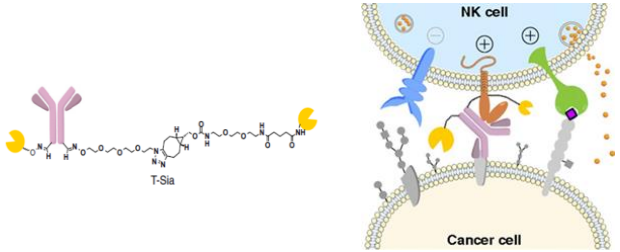
Initial Academic Concept

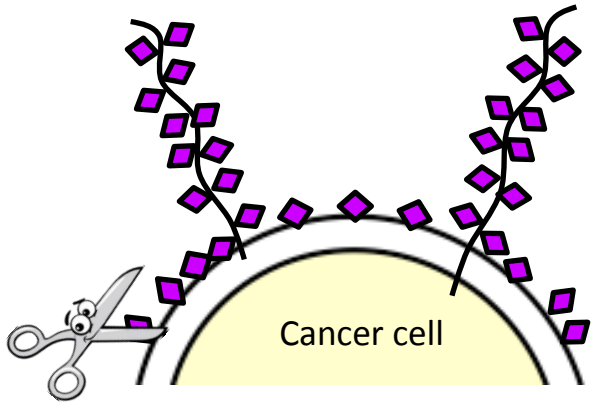
Bertozzi Lab

(Stanford University)

Bacterial Sialidase Chemical Conjugates

***In vitro* PoC**





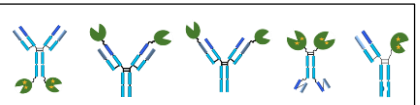
Xiao H, Woods EC, Vukojicic P, Bertozzi CR PNAS. 2016

Reduction to Practice

PALLEON PHARMACEUTICALS

Human Sialidase Genetic Fusions

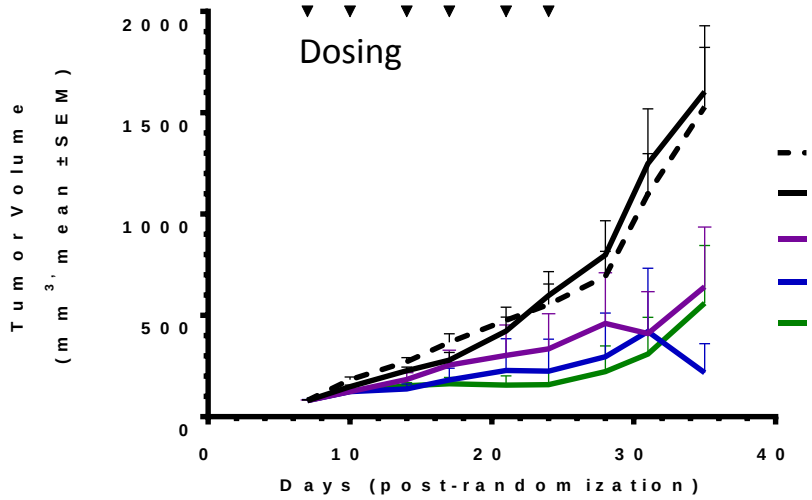
***In vivo* PoC**

Select Ideal Human Sialidase	
Improve CMC Developability	
Determine *EAGLE* Configurations	

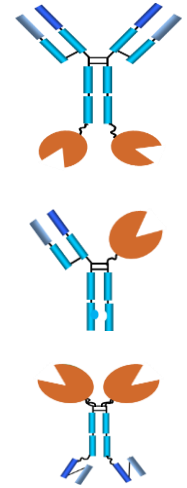
- Developability (yield, purity, stability)
- Intact Fc functions (FcRn and Fc-gamma receptors)
- Dual functions
  - Tumor-associated antigen binding arm
  - Sialidase arm
  - Targeted de-sialylation of tumor cells

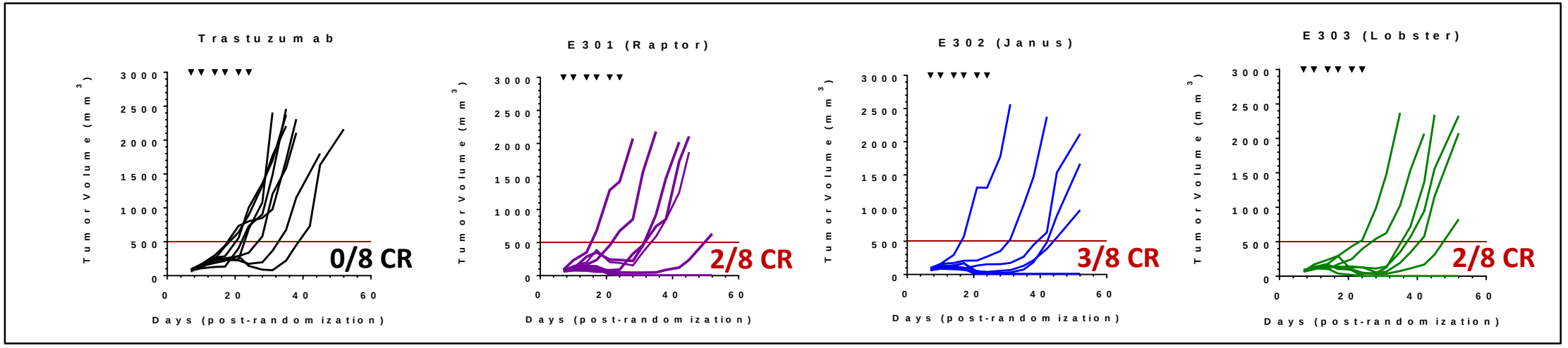
Multiple *EAGLE* Formats Achieved Single Agent Complete Regressions in Preclinical Tumor Models

Breast Cancer EMT6-Her2 Syngeneic Subcutaneous Tumor Model



n=8 mice per group
IP doses at 10mg/kg





EAGLE Reduced Tumor Cell Surface Sialic Acids Levels *in vivo*

Breast Cancer EMT6-Her2 Syngeneic Tumor Model

Balb/c

Intra mammary implantation of EMT6-Her2

Tumor ~350 mm^3

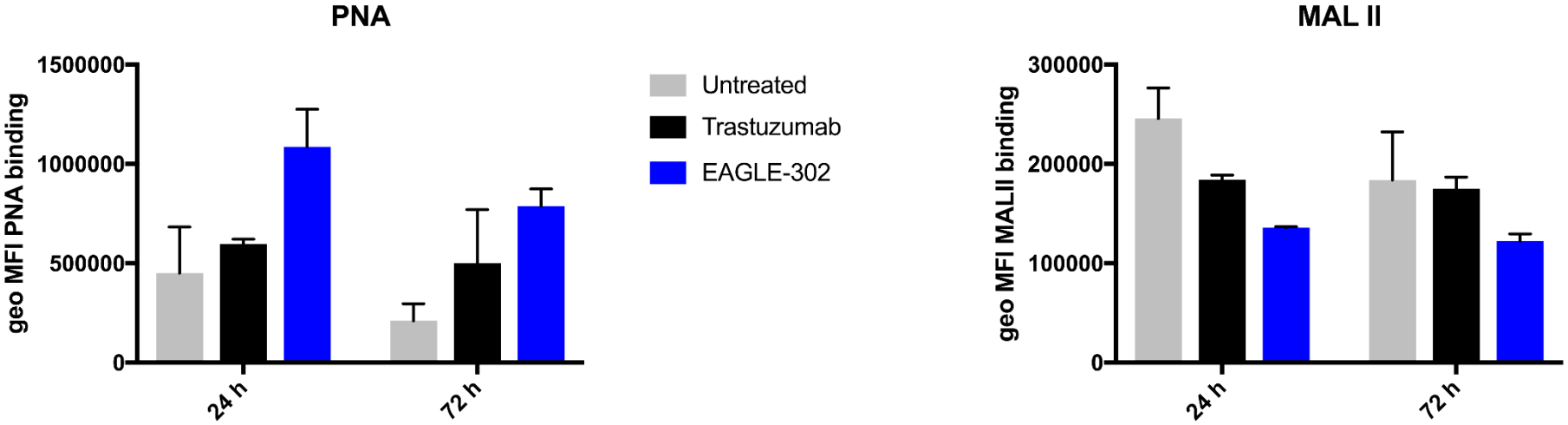
Single dose (IP, 10mg/kg)

Sacrifice & FACS analysis

24h (p.i.)

72h (p.i.)

FACS Analysis: Measure of Tumor Cells' De-Sialylation

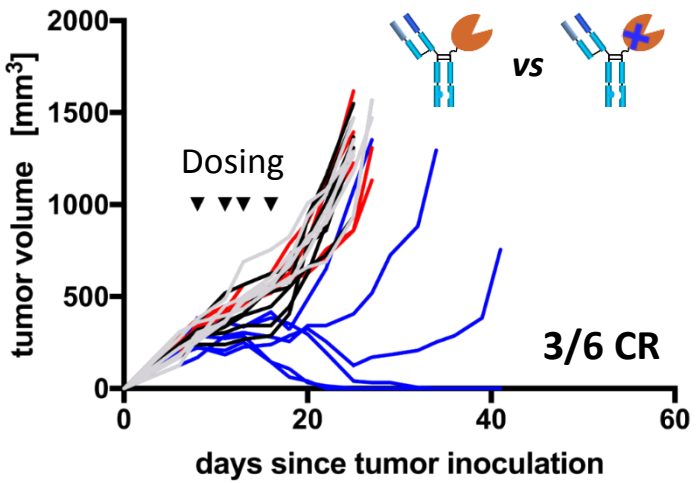


↑PNA = ↑Galactose Residues = De-sialylation

↓MAL II = ↓sialic acids = De-sialylation

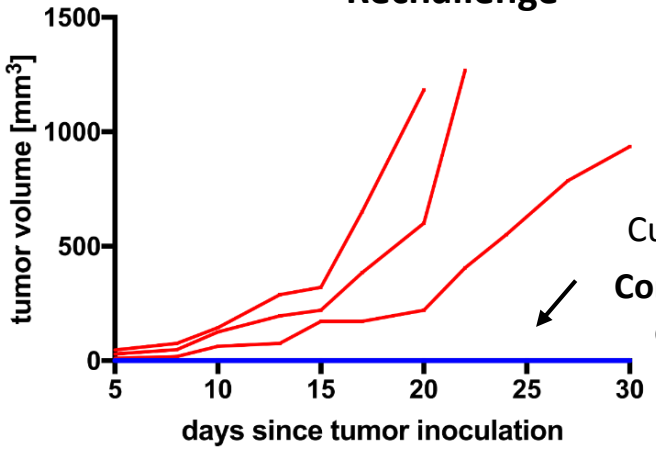
EAGLE Showed Sialidase-Dependent Efficacy, Increased Immune Cell Infiltration, and Induced Anti-Tumor Immunological Memory

Breast Cancer EMT6-Her2 Syngeneic Orthotopic Model



- Vehicle
- Trastuzumab
- *EAGLE*-302
- *EAGLE*-302 LoF (Sialidase Silent)

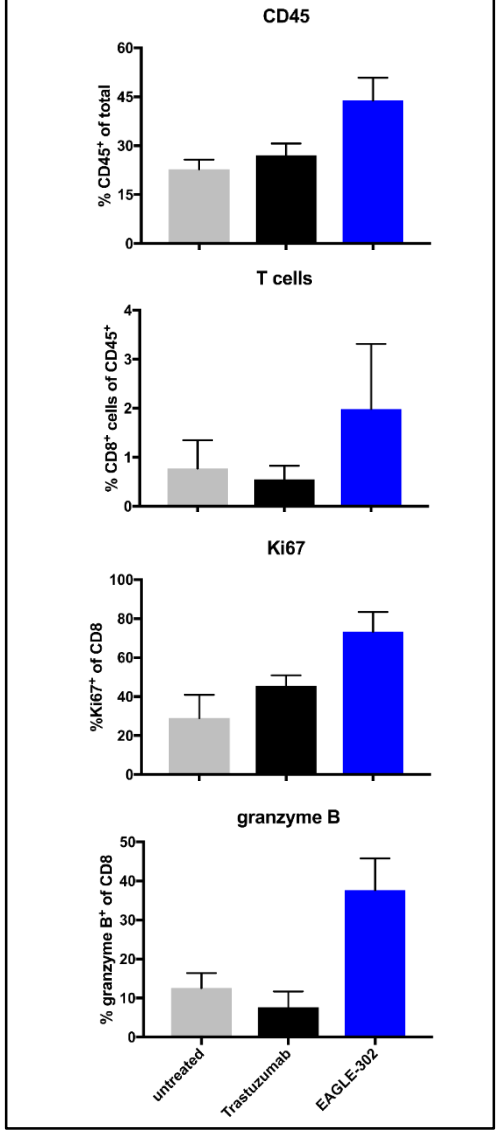
Rechallenge



- *EAGLE*-302 treated
- Naïve mice

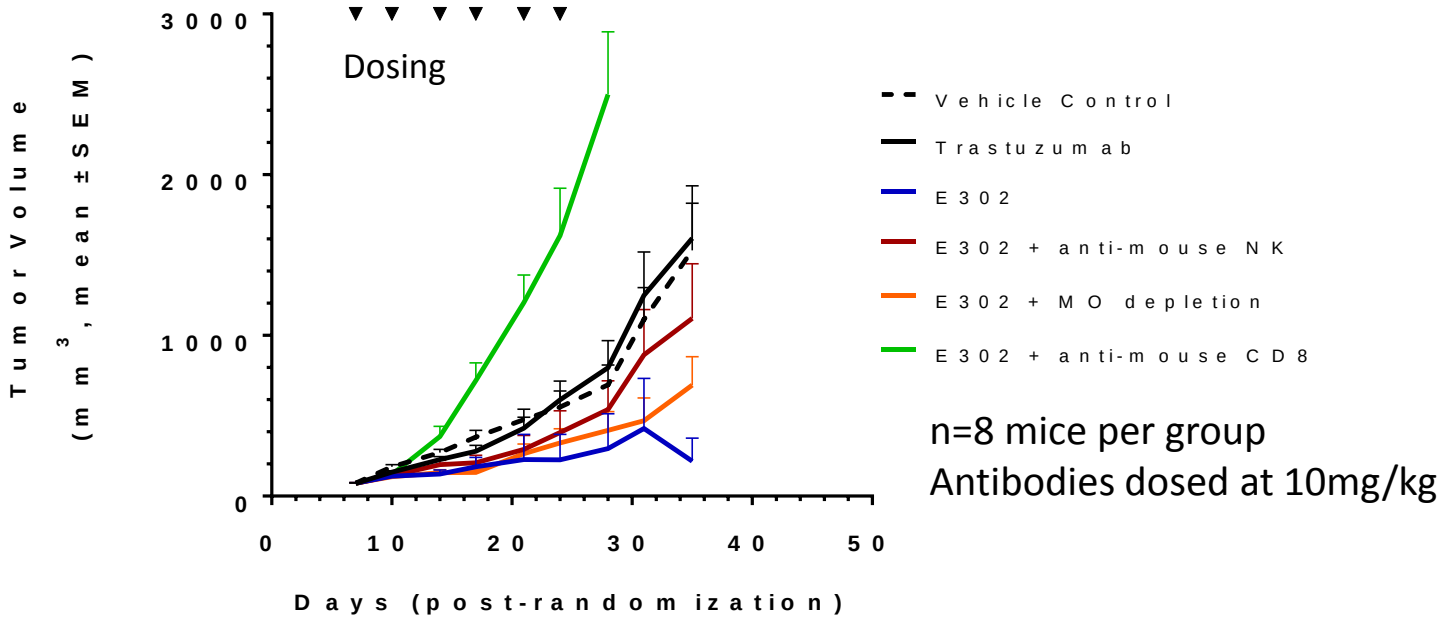
Cured Mice from *EAGLE* (n=3)

Complete Rejection of Rechallenge of EMT6-Her2 and EMT6 Cells

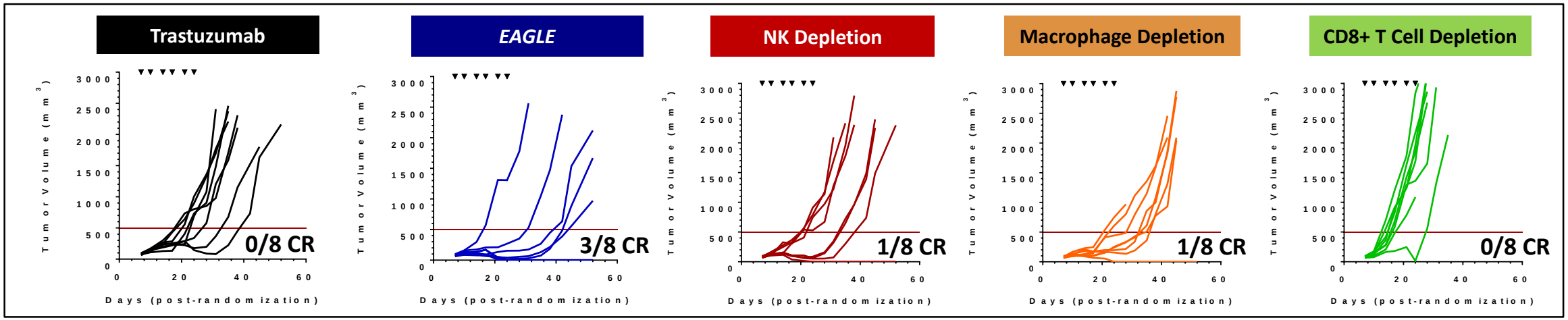


The Mechanism of Action of *EAGLE* Depends on Both Innate and Adaptive Immunity

Breast Cancer EMT6-Her2 Syngeneic Subcutaneous Tumor Model

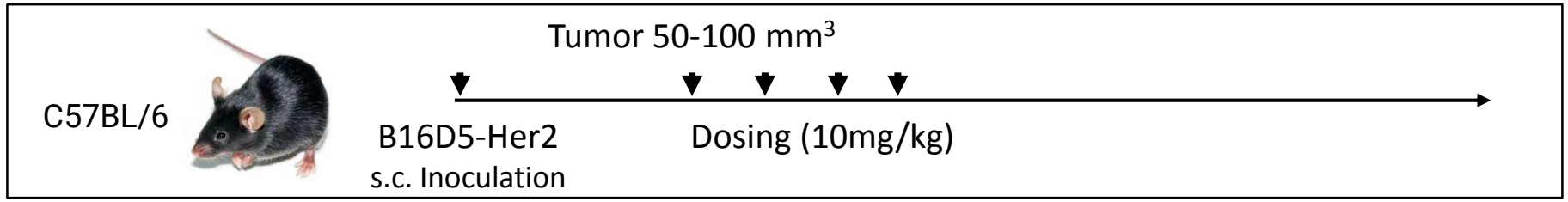


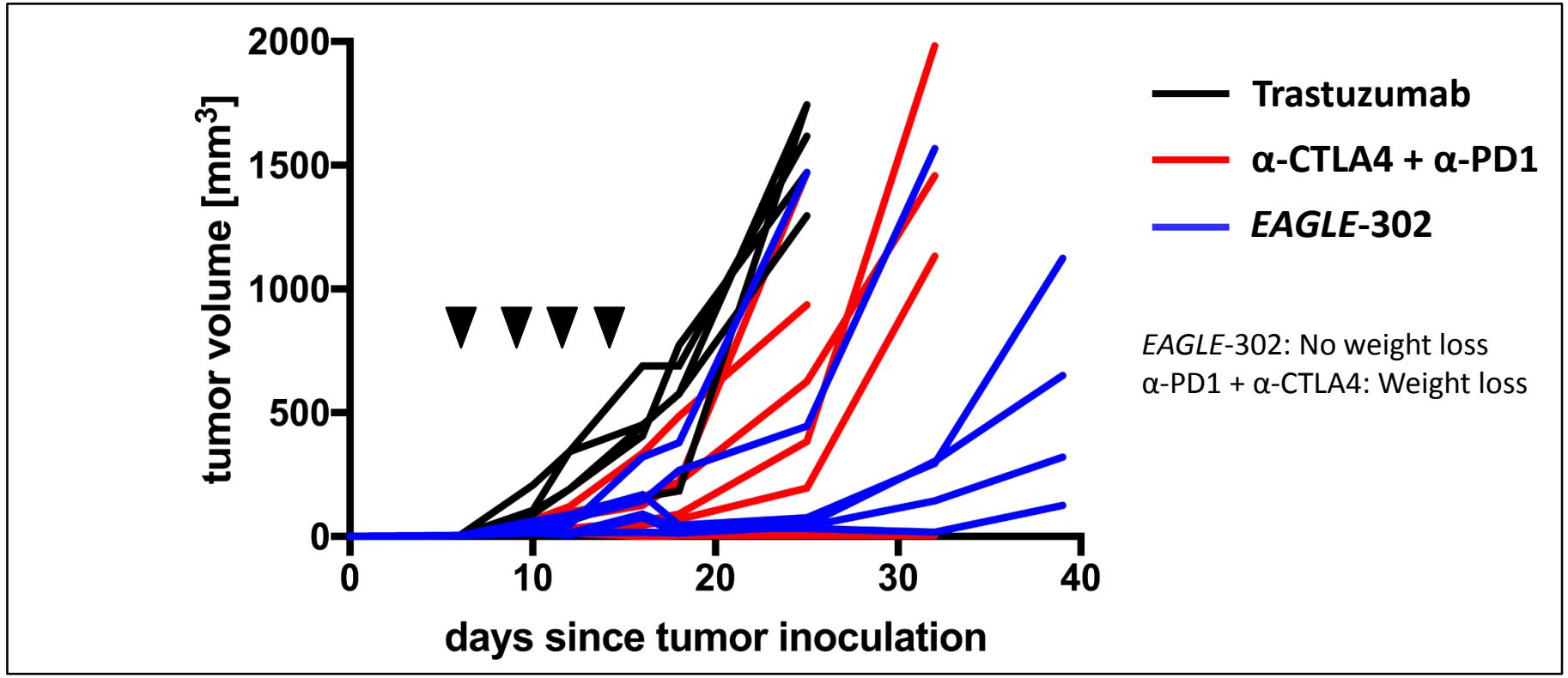
n=8 mice per group
Antibodies dosed at 10mg/kg



EAGLE has Monotherapy Efficacy Comparable to the Combination of α-PD1 and α-CTLA4 in the "Cold" Tumor B16 Model

Cold Tumor B16 Model (B16D5-Her2)



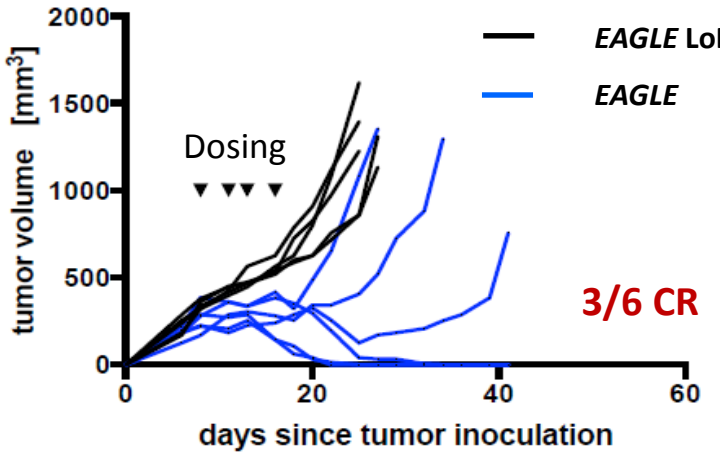


EAGLE Has Substantial Combination Efficacy with T-Cell Checkpoint Inhibition

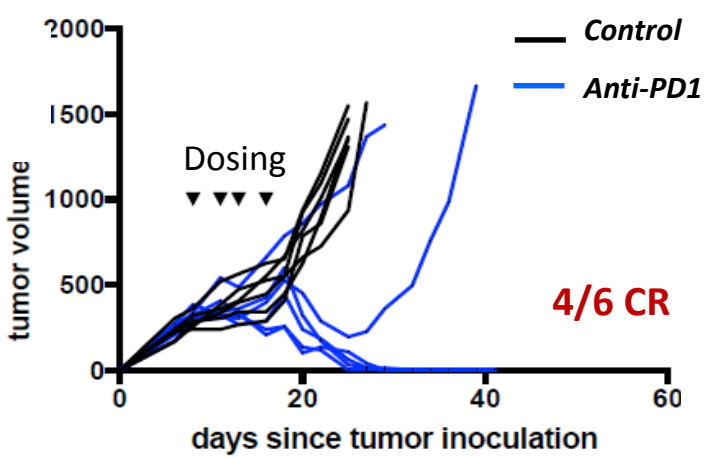
Breast Cancer EMT6-Her2 Syngeneic Orthotopic Model

Single Agent Activity

EAGLE

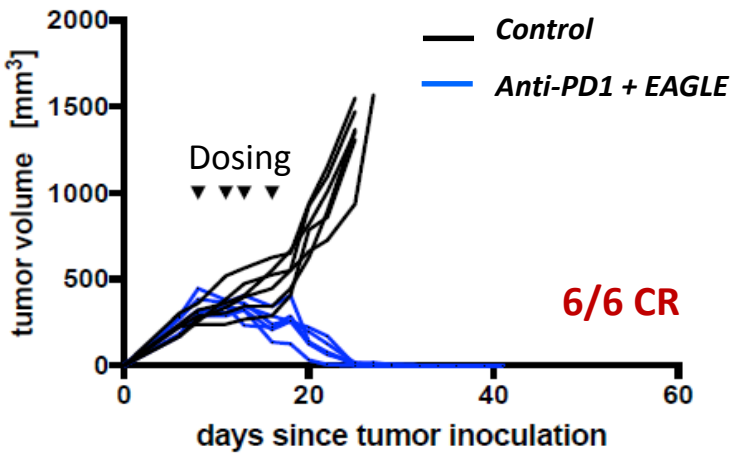


Anti-PD1



Combination

EAGLE + Anti-PD1



Summary

- **Glyco-immune checkpoints play critical roles in cancer immune evasion**
  - Innate immune response
  - Adaptive immune response
- ***EAGLE* showed compelling monotherapy efficacy in syngeneic tumor models**
  - Single agent complete regressions with immunological memory
  - Efficacious in cold tumor model
  - Striking activity in combination with PD-1/PD-L1 targeting
- ***EAGLE* platform offers novel opportunities to treat cancer targeting the glyco-immune checkpoint axis**
  - Overcomes the heterogeneity challenges of tumor sialoglycans
  - Disables immunosuppressive glycan function within the tumor microenvironment
  - Scalable, transforming TAA-targeting mAbs into immune-modulating agents

Acknowledgements

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