

XmAb808, a B7H3-targeted CD28 bispecific antibody, costimulates T cells to enhance anti-tumor activity of clinically active CD3 T cell engagers

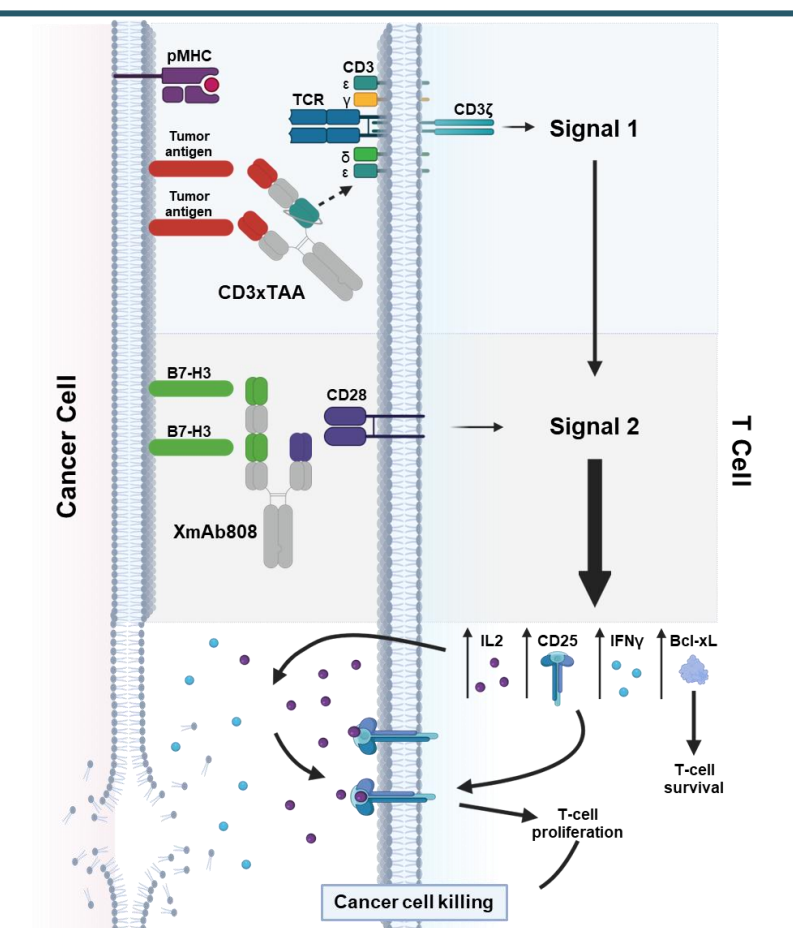


Abstract #2640

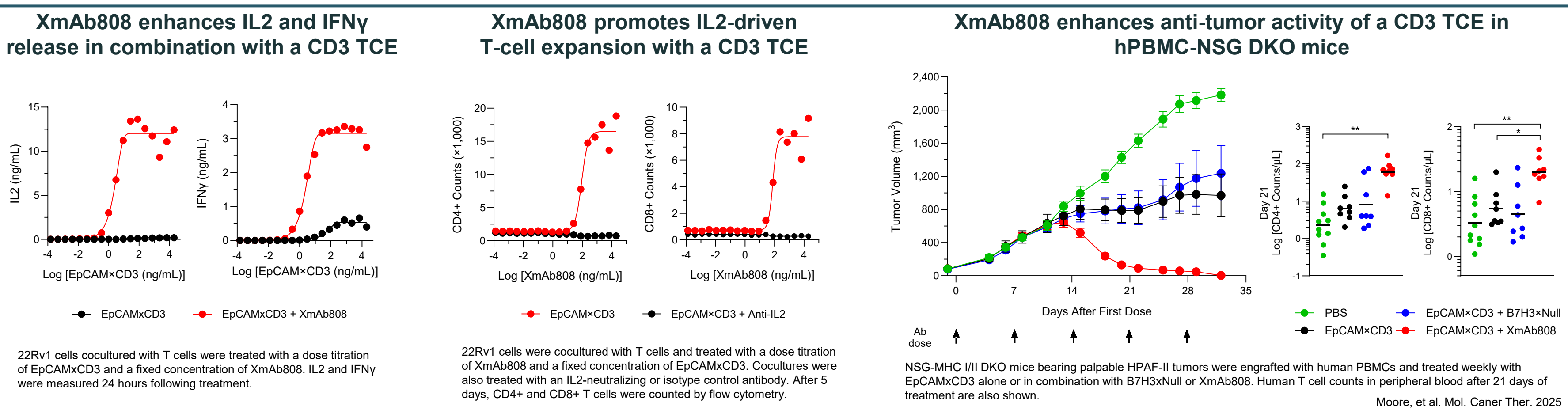
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Summary

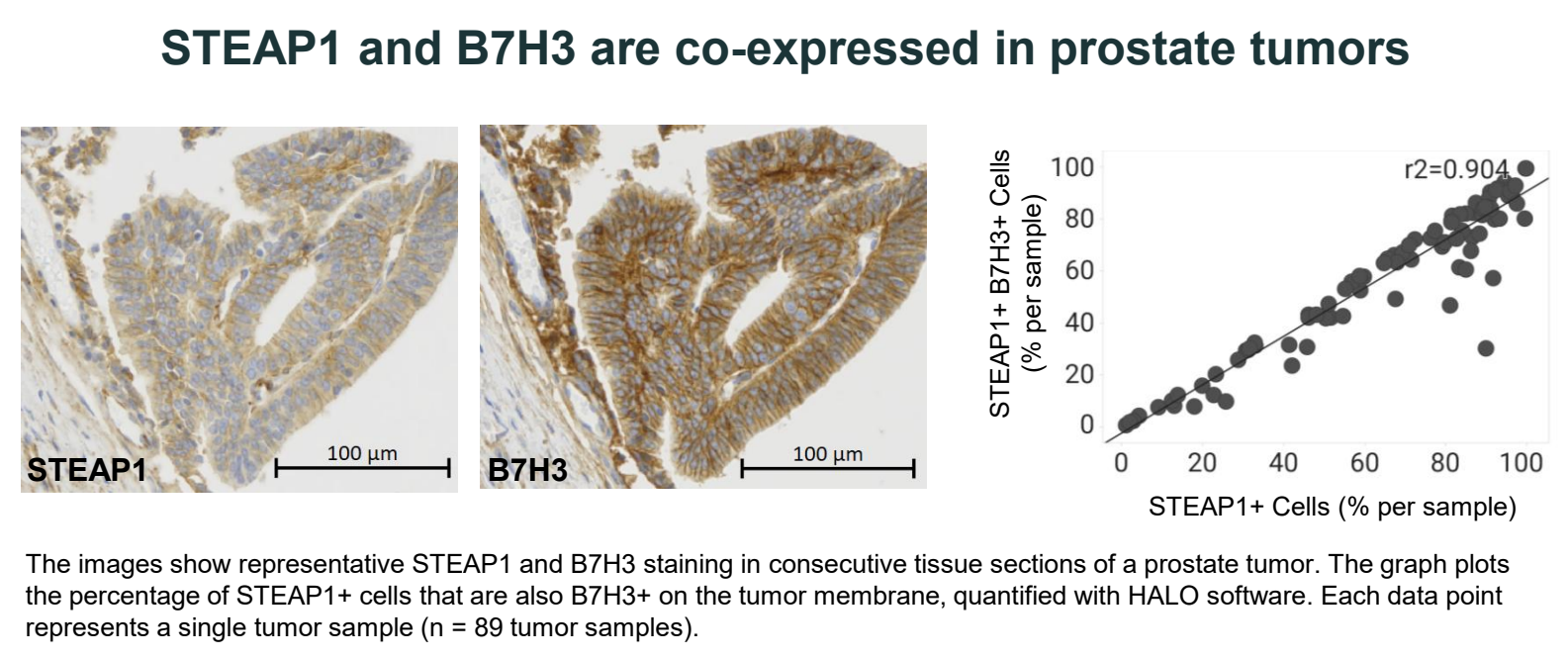
- CD3 bispecific T cell engagers (CD3 TCEs) are a promising therapeutic modality for solid tumors, with multiple candidates in clinical development.
- CD3 TCEs bridge tumor-associated antigens and CD3 on T cells to form an immune synapse, delivering Signal 1 for T cell activation.
- Solid tumors, unlike professional antigen-presenting cells, typically lack CD28 ligands required for Signal 2 costimulation. T cells receiving Signal 1 without Signal 2 costimulation risk developing anergy, potentially limiting CD3 TCE efficacy.
- We developed XmAb808, a novel 2+1 B7H3 x CD28 bispecific incorporating a non-superagonistic, monovalent CD28-binding domain and a high-avidity, bivalent B7H3-binding domain.
- XmAb808 amplifies the in vitro and in vivo antitumor activity of clinically active CD3 TCEs, including XmAb541 (CLDN6xCD3), XmAb819 (ENPP3xCD3), and a Xaluritamig analog (STEAP1xCD3).
- These preclinical data support the clinical development of XmAb808 in combination with CD3 TCEs.



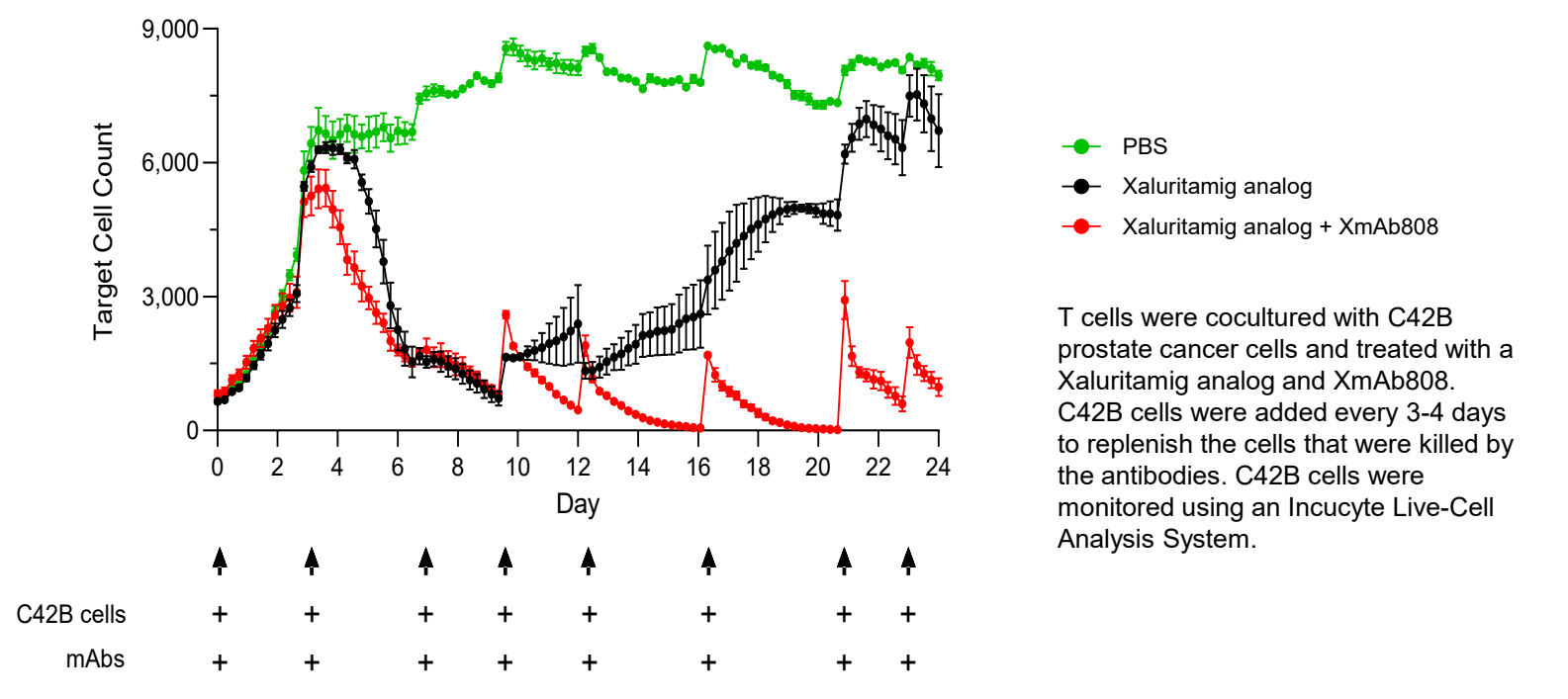
XmAb808 enhances the activity of a prototype CD3 TCE



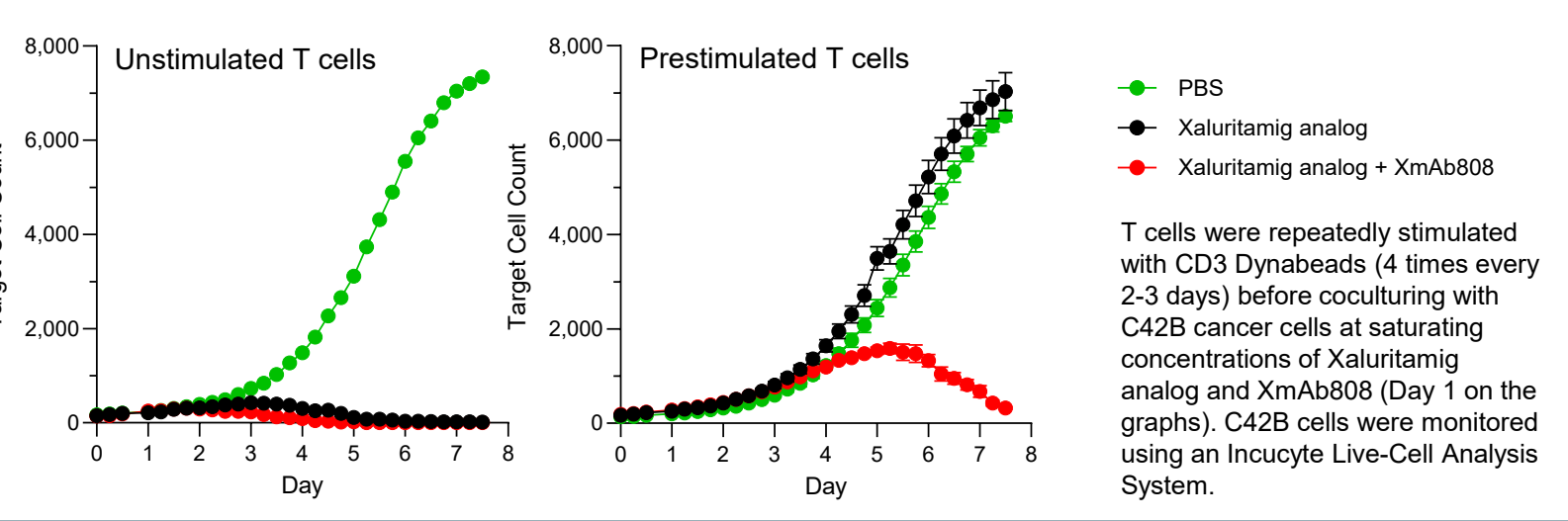
XmAb808 enhances the activity of a Xaluritamig analog (STEAP1xCD3)



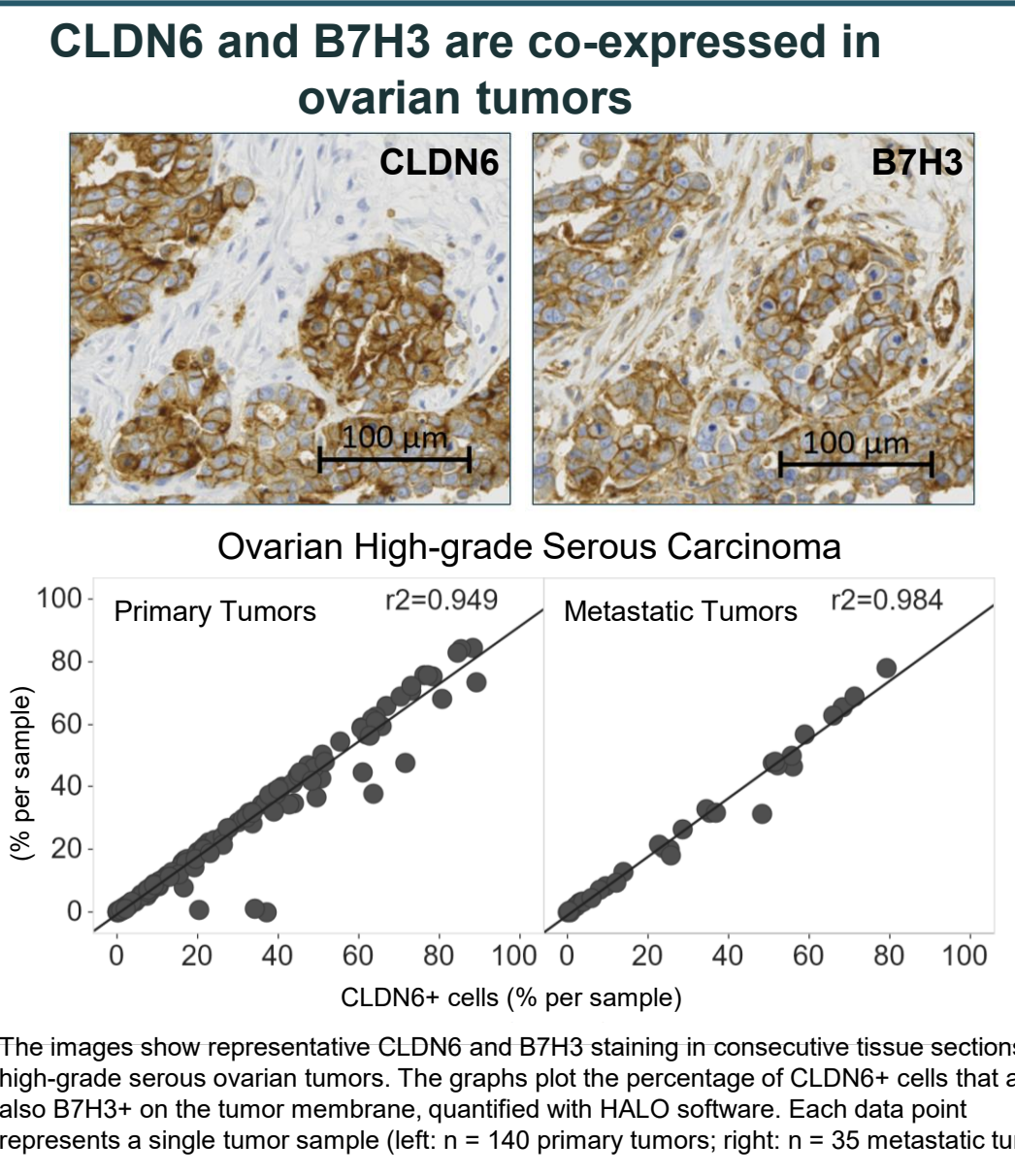
XmAb808 promotes durable T-cell-directed killing of cancer cells with a Xaluritamig analog



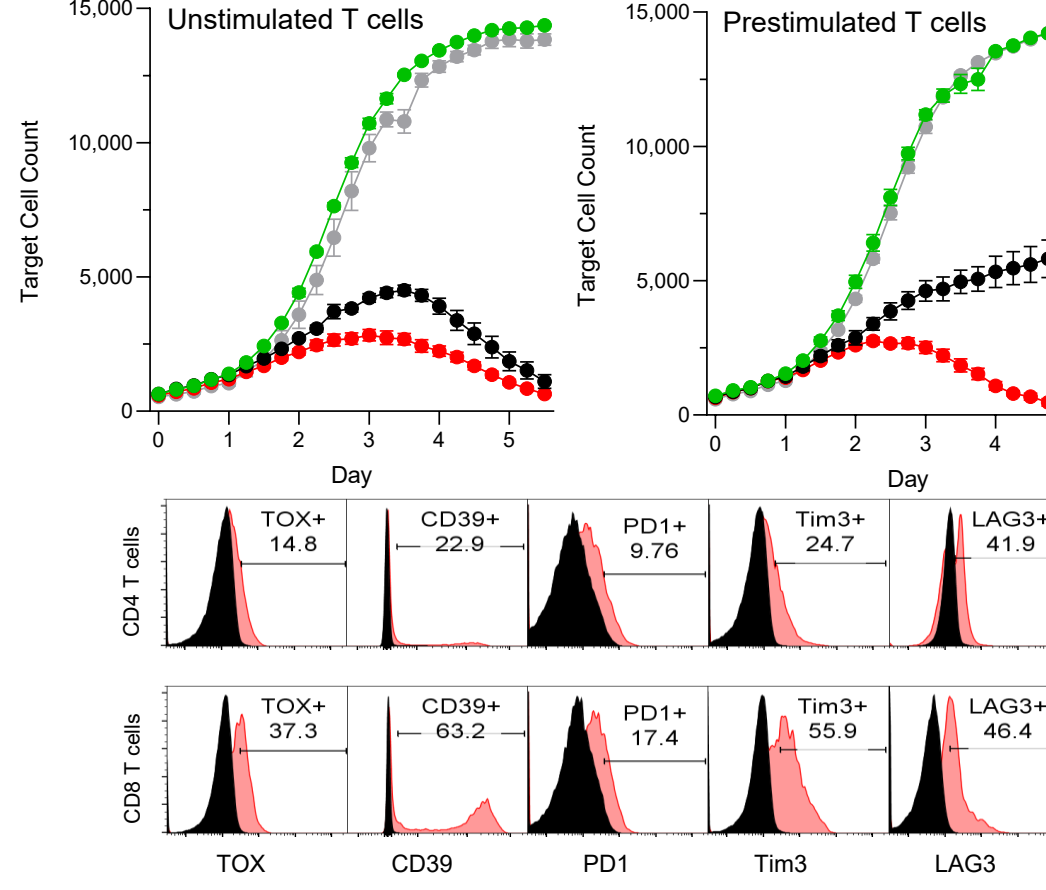
XmAb808 restores activity of a Xaluritamig analog in exhausted T cells



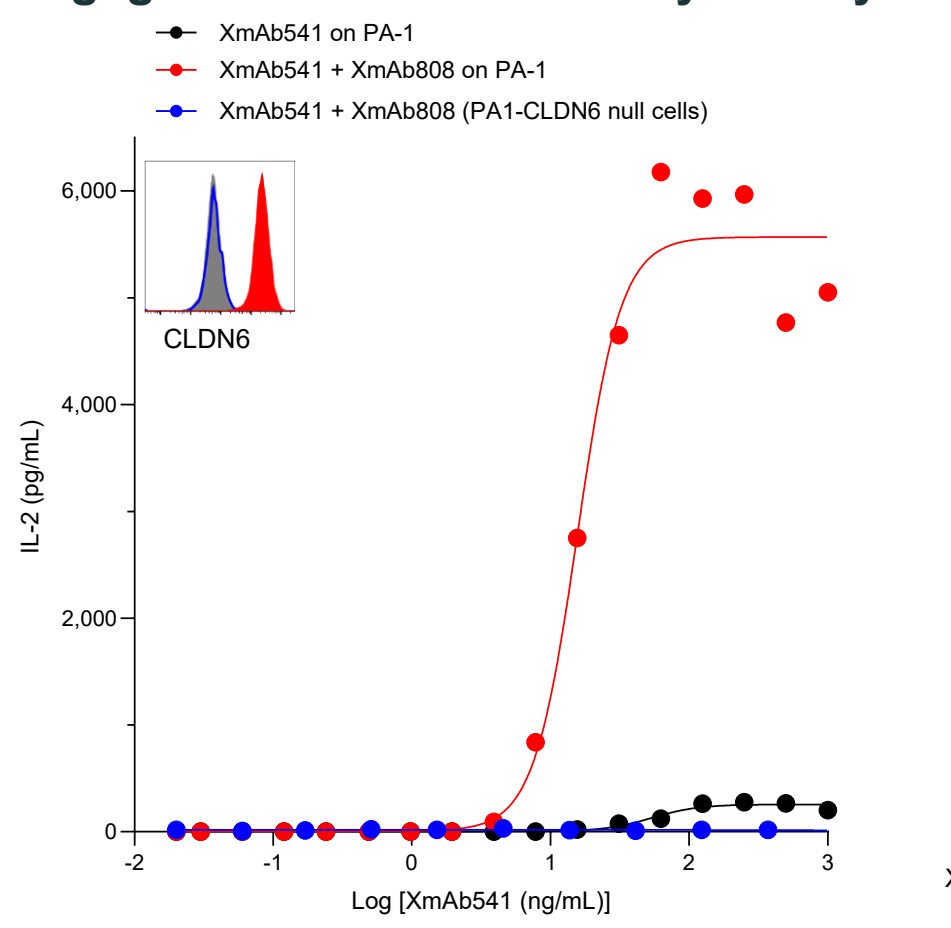
XmAb808 enhances XmAb541 (CLDN6xCD3) activity



XmAb808 enhances XmAb541-induced killing in exhausted T cells

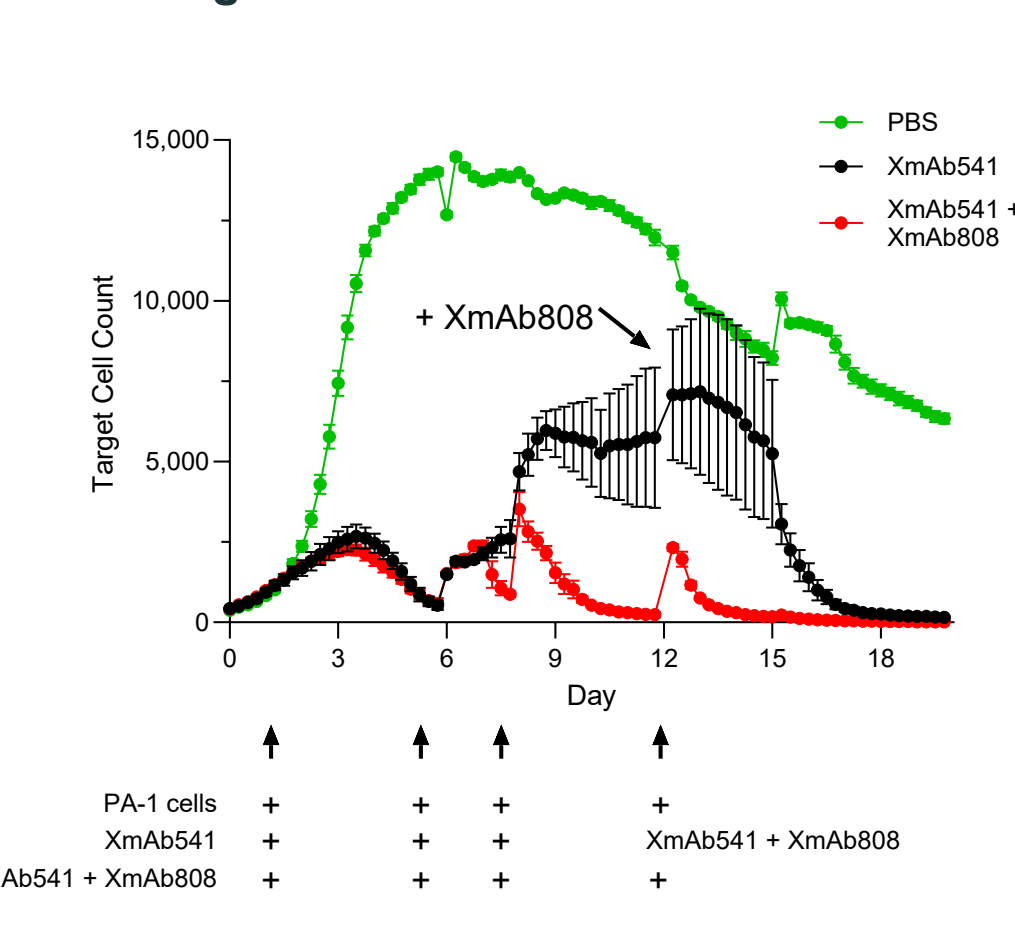


XmAb808 requires CD3 TCE engagement for costimulatory activity



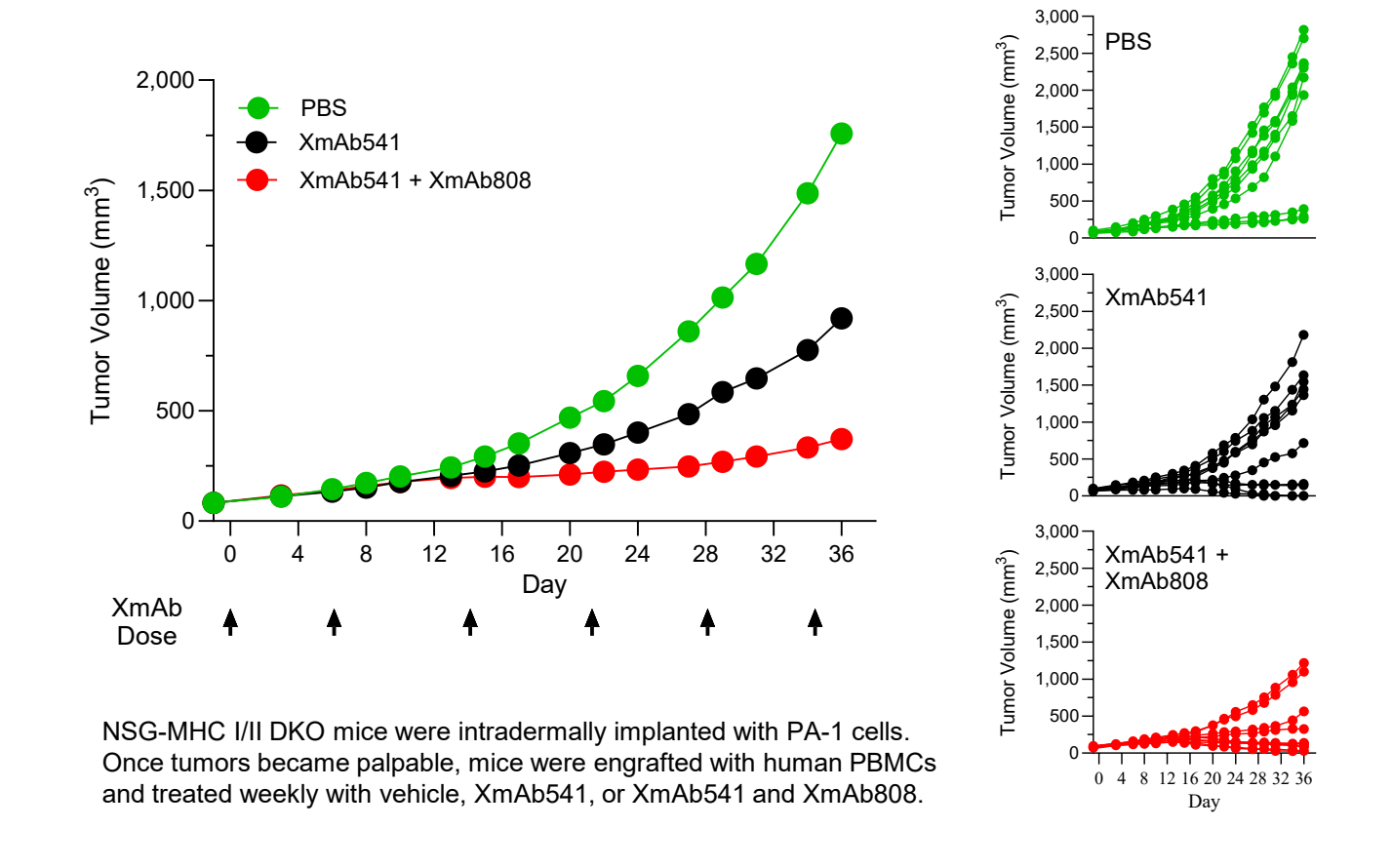
T cells were cocultured with PA-1 or PA-1-CLDN6-null cells and treated with a dose titration of XmAb541 and a fixed concentration of XmAb808. IL2 release was measured 24 hours following treatment.

XmAb808 promotes durable T-cell-directed killing of cancer cells with XmAb541



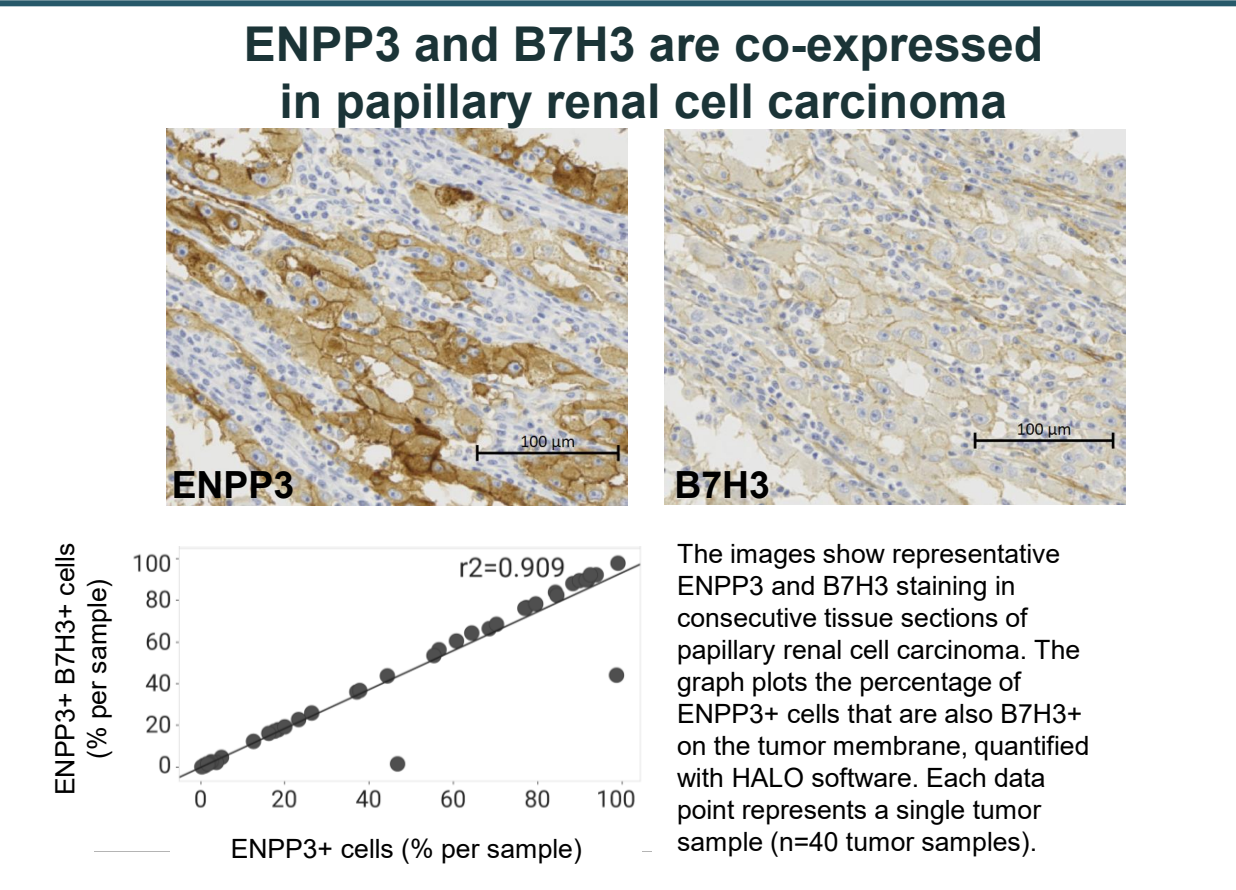
Cocultures of T cells and PA-1 cells were treated with XmAb541 and XmAb808. PA-1 cell viability was monitored in real time using an Incucyte Live-Cell Analysis System. PA-1 cells were added when complete cell depletion was observed.

XmAb808 enhances anti-tumor activity of low dose XmAb541

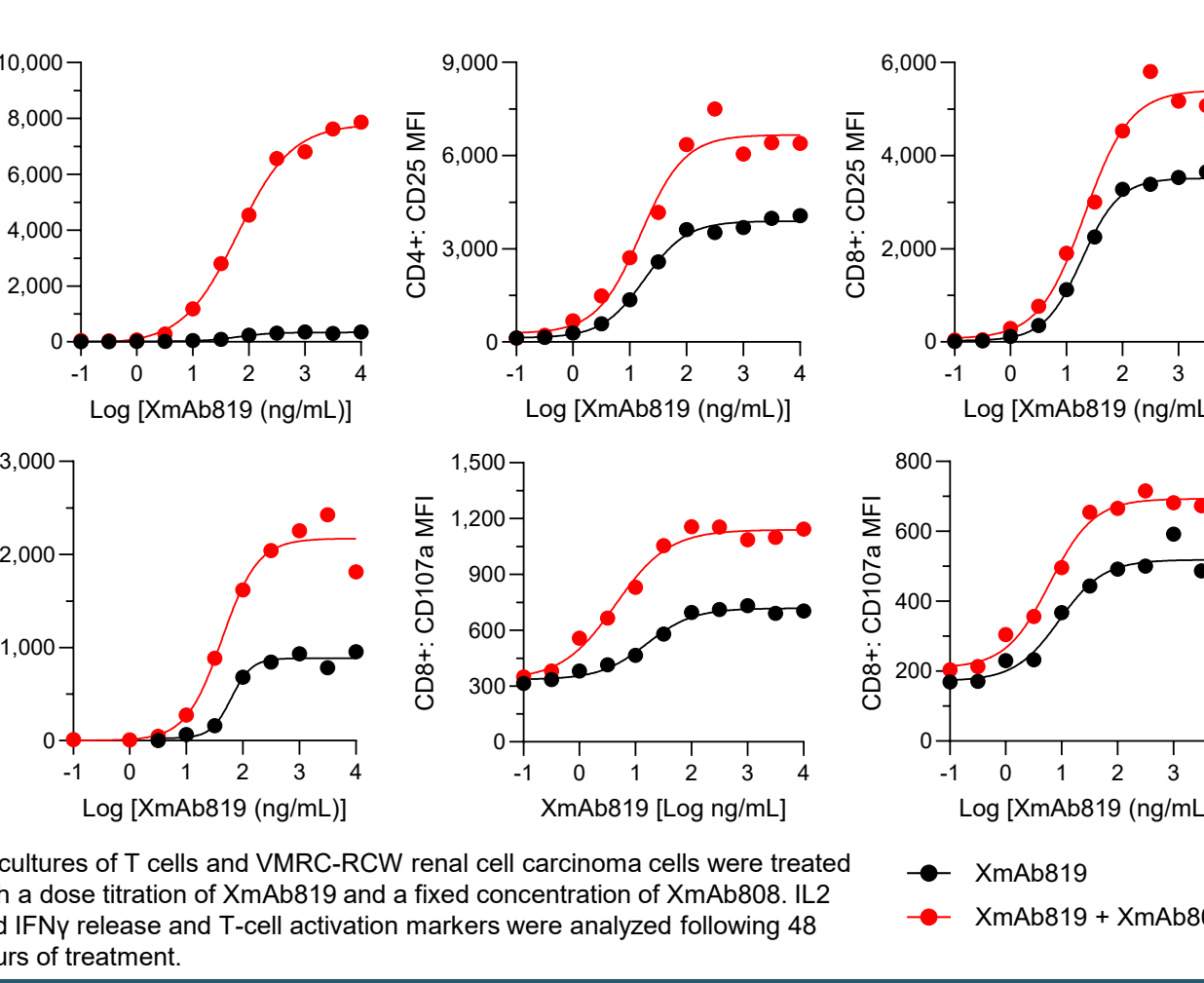


NSG-MHC-III DKO mice were intradermally implanted with PA-1 cells. Once tumors became palpable, mice were engrafted with human PBMCs and treated weekly with vehicle, XmAb541, or XmAb541 + XmAb808.

XmAb808 enhances XmAb819 (ENPP3xCD3) activity



XmAb808 enhances the activity of XmAb819 in vitro



Cocultures of T cells and VMRC-RCW renal cell carcinoma cells were treated with a dose titration of XmAb819 and a fixed concentration of XmAb808. IL2 and IFNγ release and T-cell activation markers were analyzed following 48 hours of treatment.

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