

Jin Qian¹, Bruce Daugherty^{2*}, Chenkai Ma³, Quin T. Waterbury¹, Xiaofei Zhi¹, Christine S. Moon¹, Ruhong Tu¹, Hiroki Kobayashi¹, Feijing Wu¹, Biyun Zheng¹, Yi Zeng¹, Hualong Zheng¹, Yosuke Ochiai¹, Ruth A. White¹, David W. Harle¹, Jonathan S. LaBella¹, Leah B. Zamechek¹, Lucas ZhongMing Hu¹, Ryan H. Moy¹, Arnold S. Han¹, Mayanka Awasthi⁴, Jennifer Cho⁴, Nelson Martinez⁴, Bernd Meibohm⁵, Natasza Ziolkowska⁴, Christopher Cooper⁴, Sina Bavari⁴, Seth Lederman², Timothy C. Wang¹ *Presenting author

¹Irving Cancer Research Center, Columbia University Medical Center, New York, NY USA; ²Tonix Pharmaceuticals, Inc., Berkeley Heights, NJ, USA; ³Integrated Diagnostic, Human Health, Health and Biosecurity, CSIRO, Westmead, NSW, Australia; ⁴Tonix Pharmaceuticals, Inc., Frederick, MD, USA; ⁵University of Tennessee Health Science Center, Memphis, TN, USA

Background

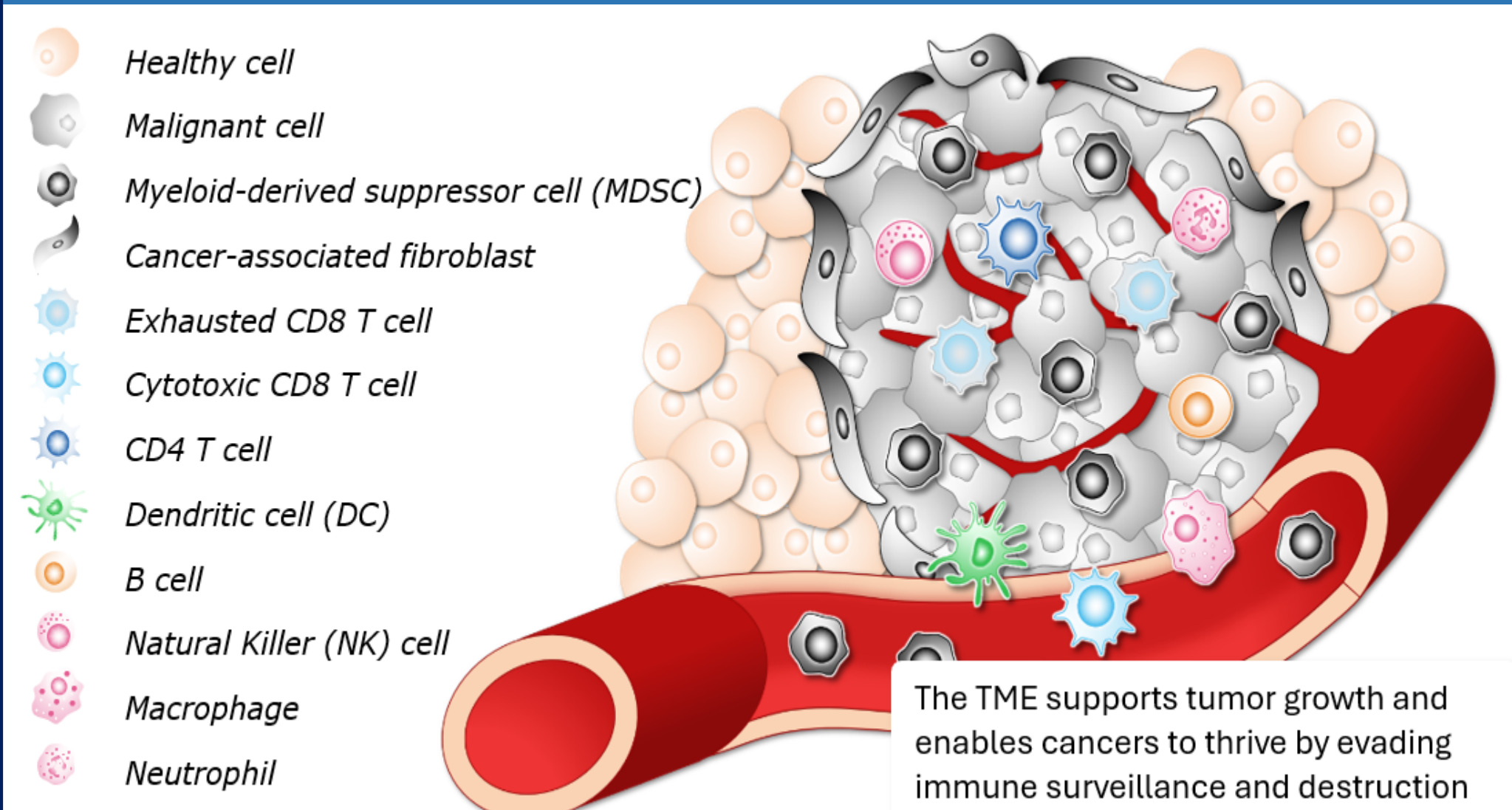
- The CXCR4-CXCL12 axis is a key regulator of hematopoiesis, immune cell trafficking, and myeloid homeostasis
- Gastric cancer disrupts normal myelopoiesis, driving expansion of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) that suppress anti-tumor immunity
- Elevated PMN-MDSCs are associated with resistance to immune checkpoint blockade and poor clinical outcomes

Hypothesis

- We hypothesized that restoring physiologic CXCR4 signaling through partial agonism would normalize cancer-driven myelopoiesis, reduce PMN-MDSC accumulation, and enhance anti-tumor immunity in gastric cancer

Introduction

Tumors Create a Toxic, Immunosuppressive Microenvironment (TME)



- Tumors are surrounded by endothelial and stroma cells, and invading immune cells, both innate and adaptive^{1,2}
- Complex regulatory network supports tumor growth, enabling cancers to thrive by evading immune surveillance and destruction^{2,3}
- The TME sabotages tumor-killing cytotoxic CD8 T cells¹
- Myeloid-derived suppressor cells (MDSCs) interfere with anticancer immunity^{2,3}

Results

Figure 1. Decline of TFF2 Correlates with CXCR4+ MDSC Expansion and Poor Survival in Gastric Cancer

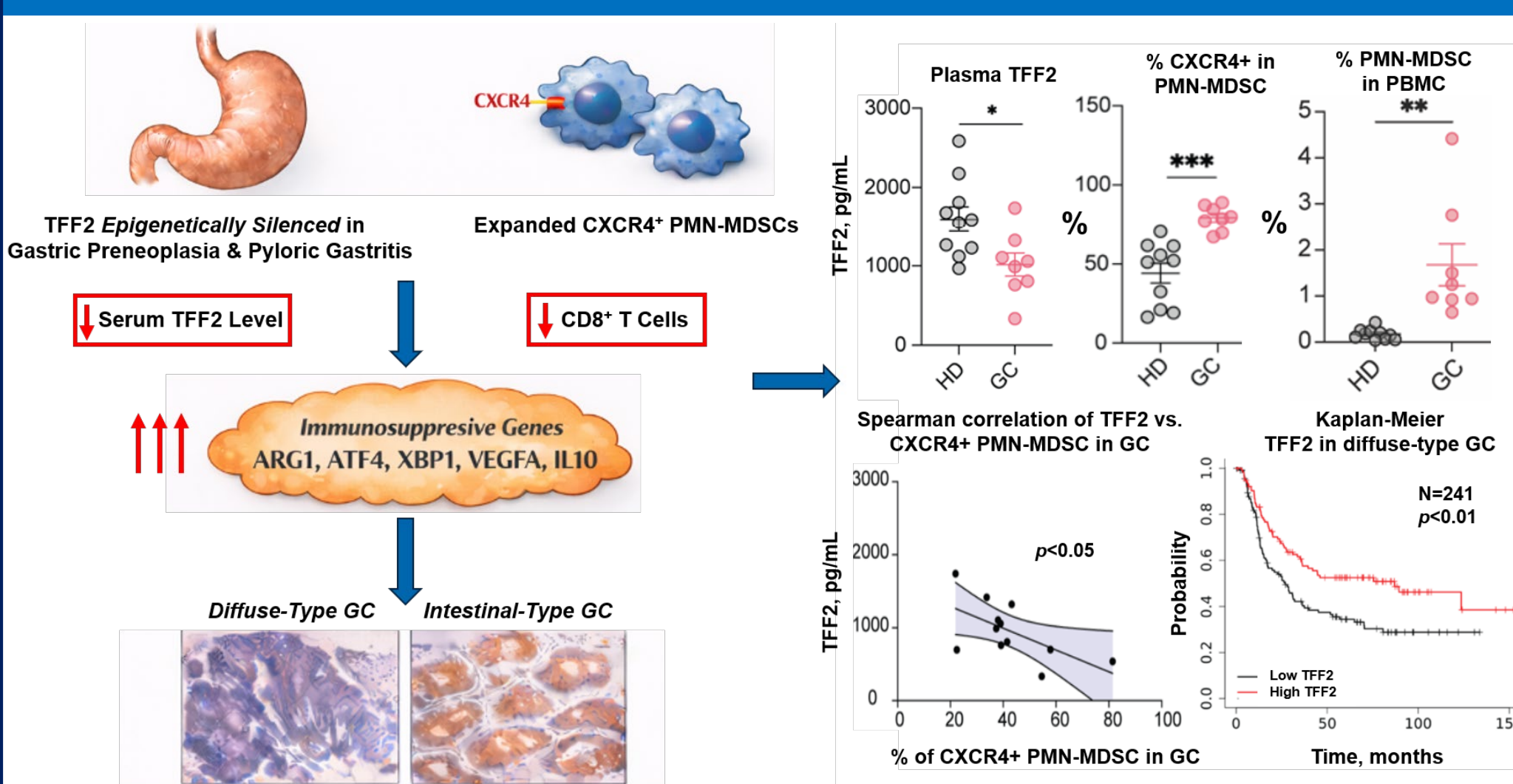


Figure 2. TNX-1700 is a Fusion Protein of Trefoil Factor-2 (TFF2) and Human Serum Albumin (HSA)

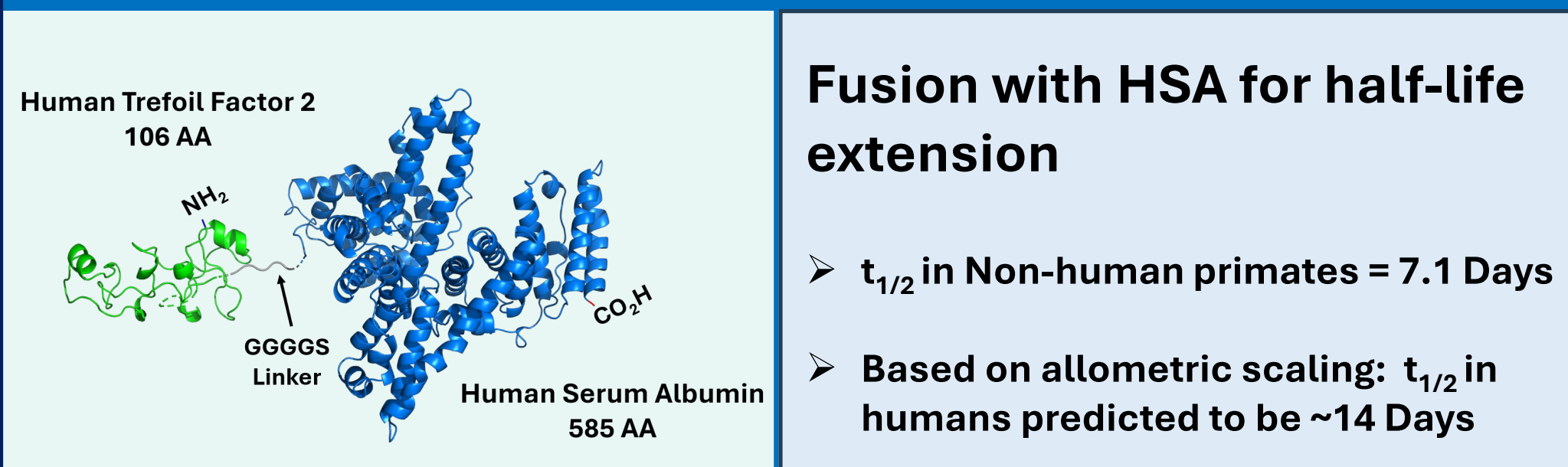
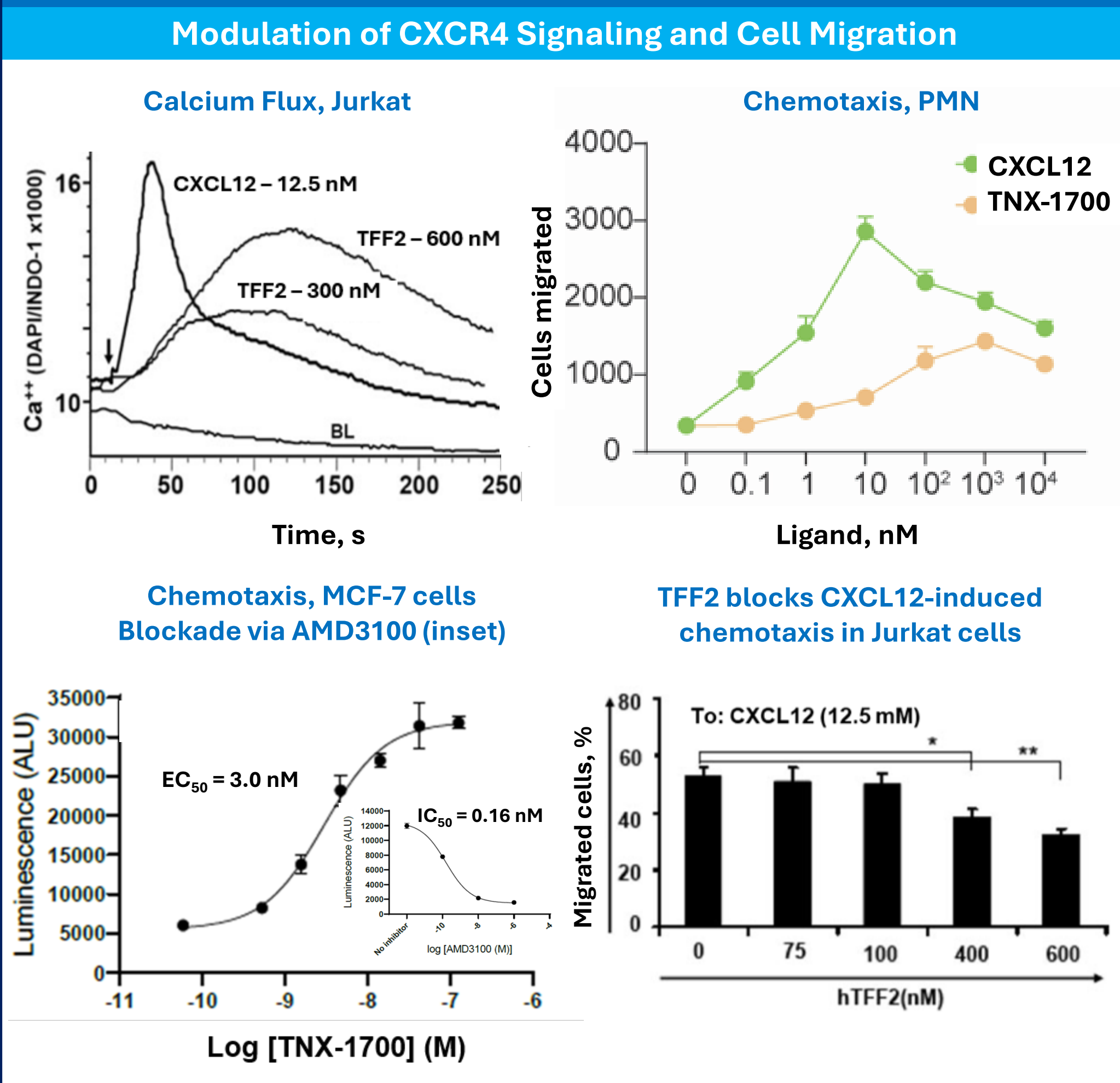


Figure 3. TNX-1700 and TFF2 are Partial Agonists on CXCR4



TNX-1700 Normalizes CXCR4 Signaling in Both the Bone Marrow and Tumor Microenvironment

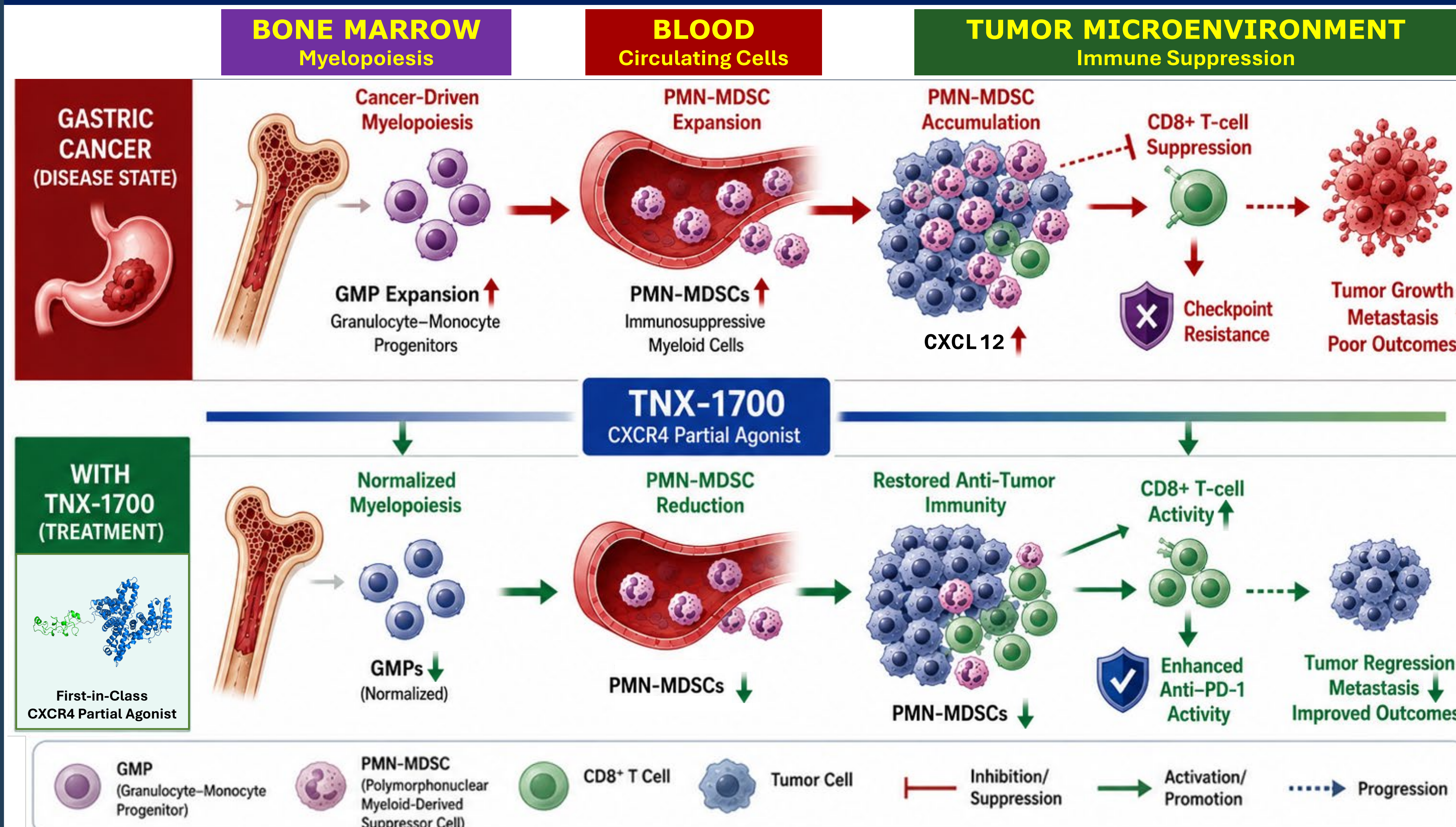
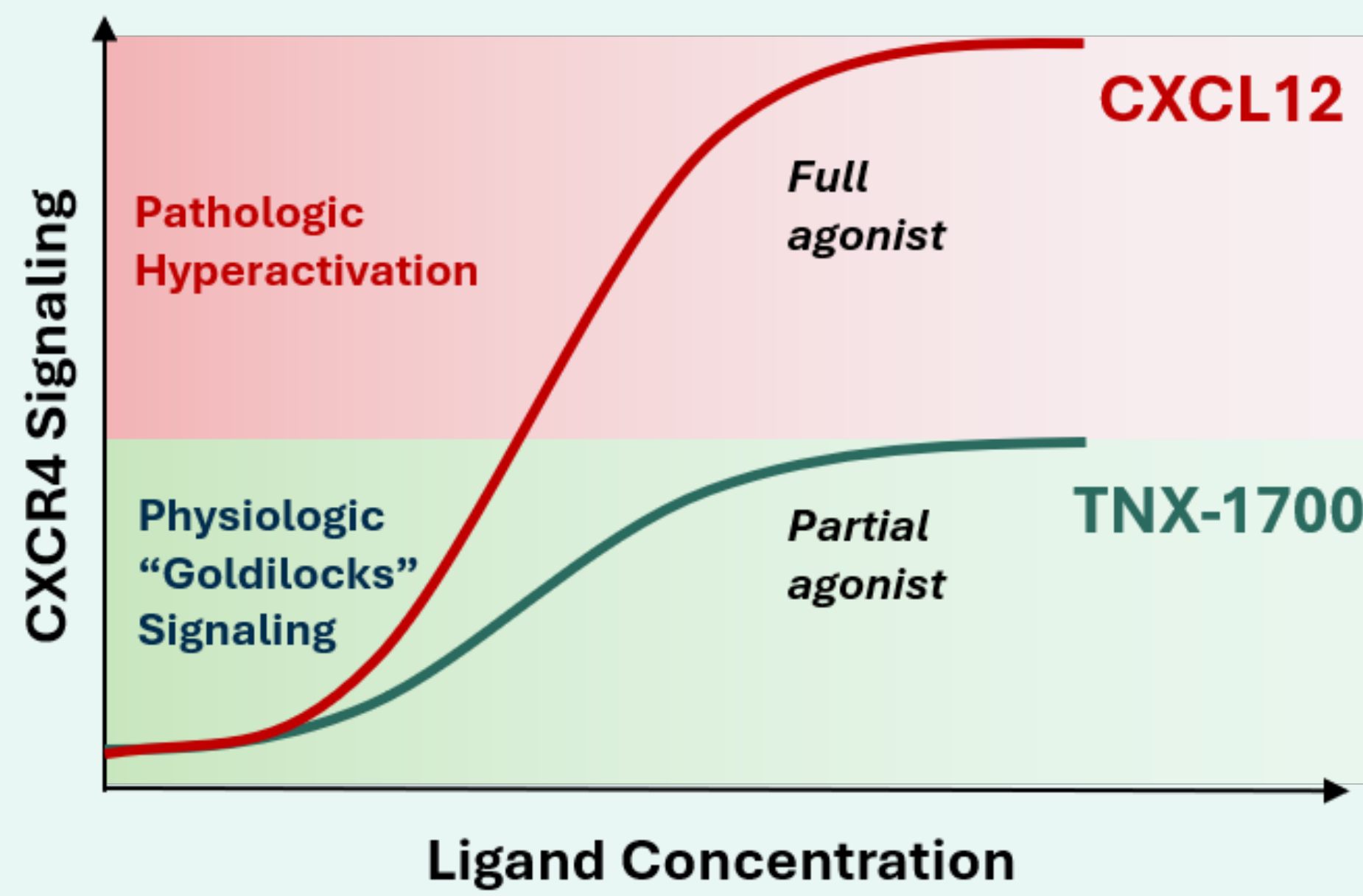


Figure 4. Goldilocks Regulation of CXCR4 Signaling

- Balanced CXCR4 activity required for normal hematopoiesis and anti-tumor activity
- Normal physiological CXCR4 levels maintain HSC homeostasis



Efficacy of TNX-1700 in Multiple Murine Models of Gastric Cancer

Figure 5. TNX-1700 Exhibits Robust Synergy with Checkpoint Blockade in ACKP Syngeneic Gastric Cancer Model

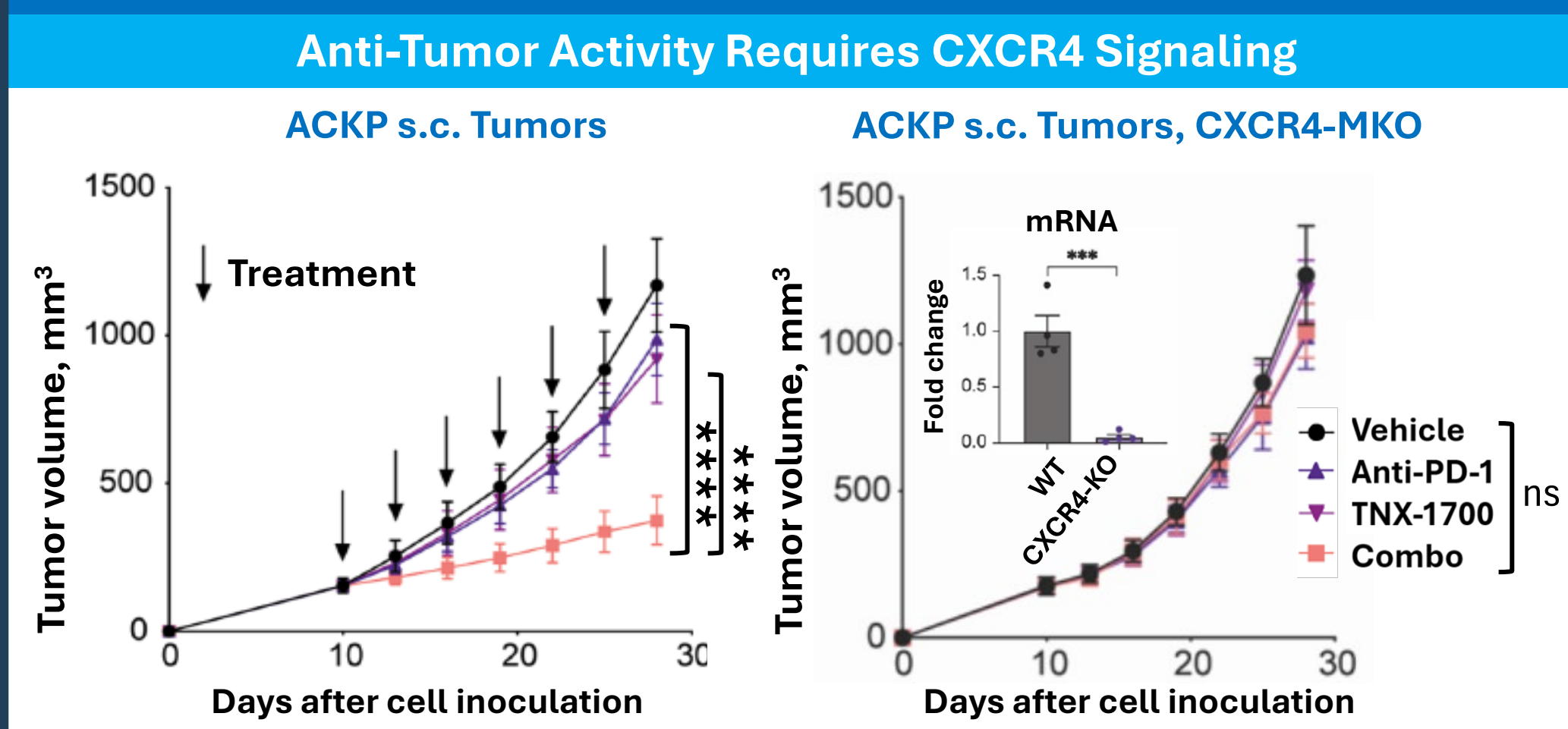


Figure 6. Combination Therapy Eradicates Established ACKP-Luc Orthotopic Gastric Cancer Tumors

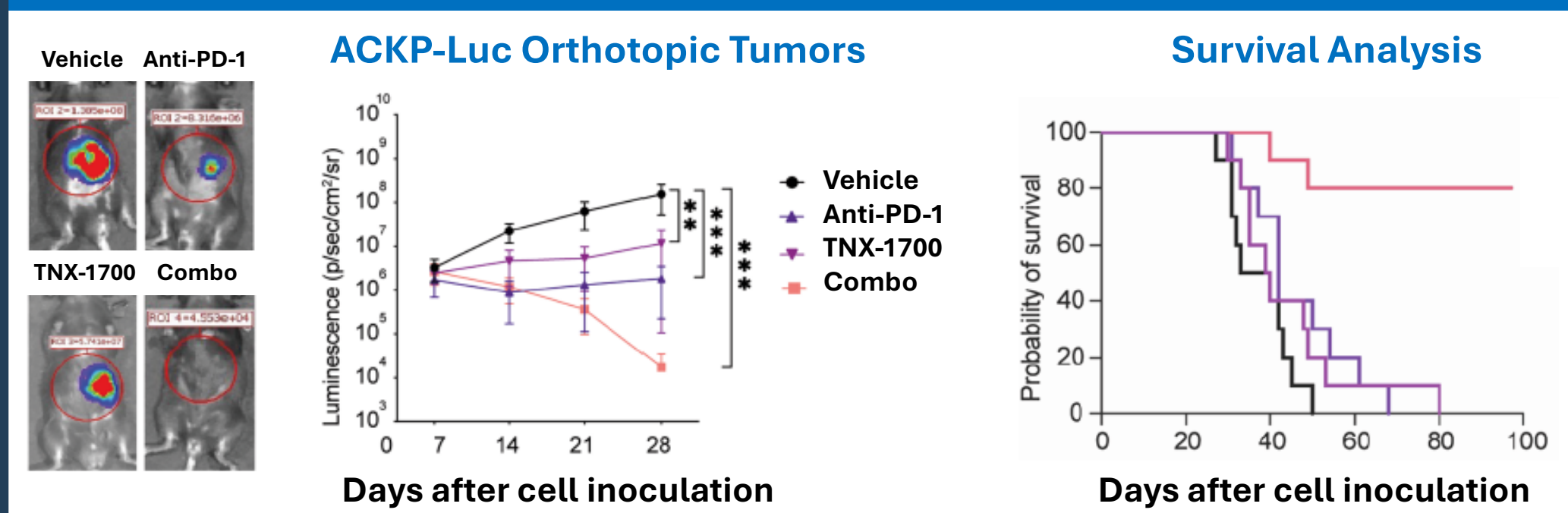


Figure 7. TNX-1700 Inhibits Tumor Invasion in Autochthonous "Diffuse-Type" Gastric Cancer Model

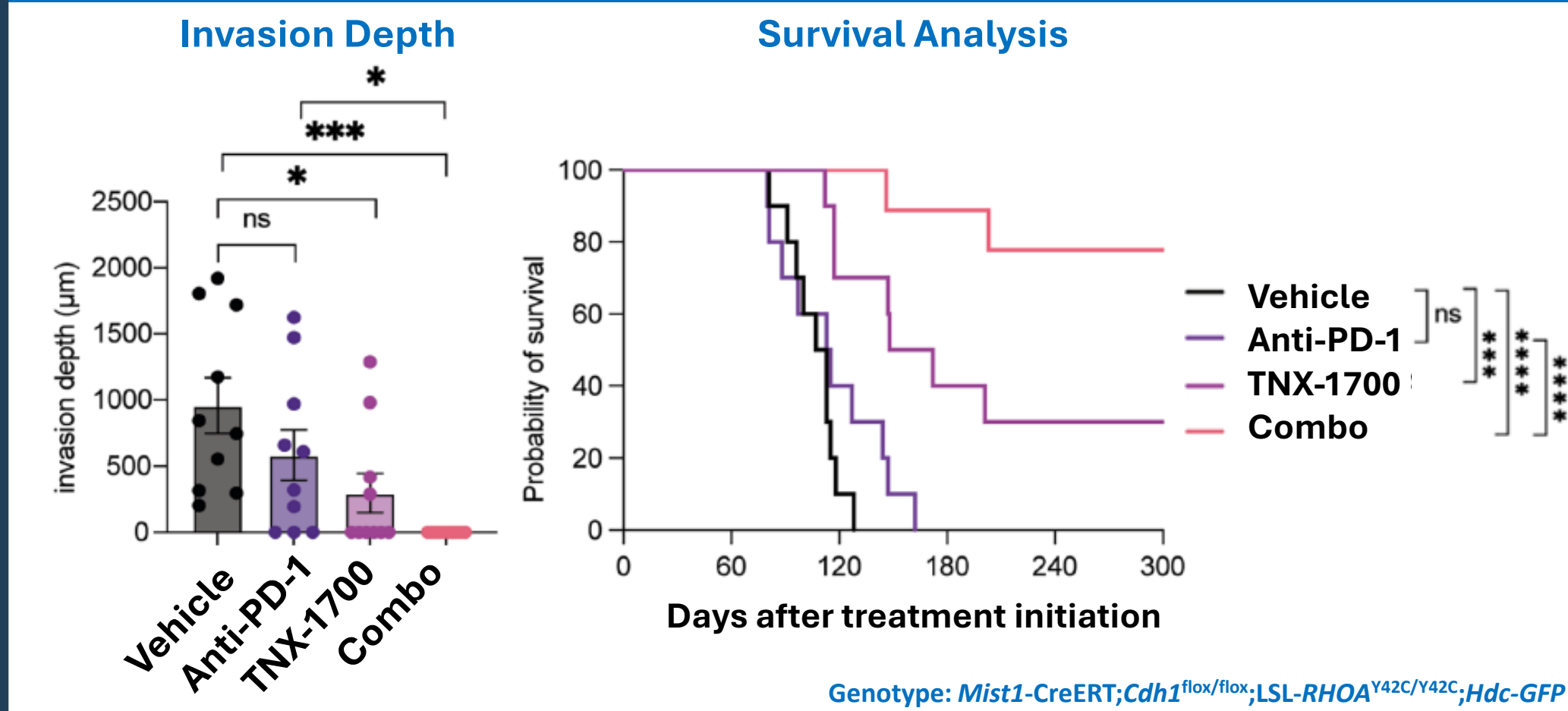


Figure 8. TNX-1700 Suppresses Metastasis in ACKP Model

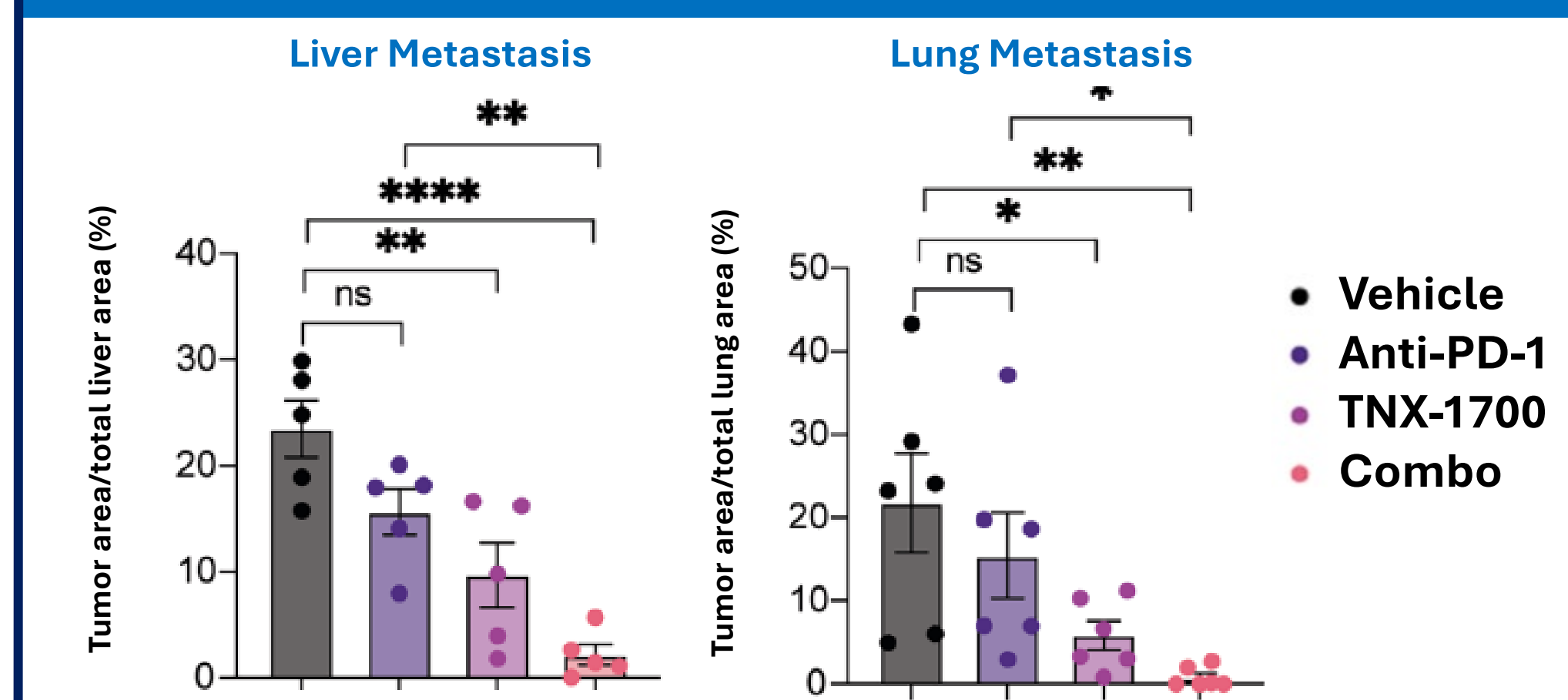


Figure 9. TNX-1700 Reduces Intratumoral and Circulating MDSCs and Reverses Cancer-Driven Expansion of GMPs

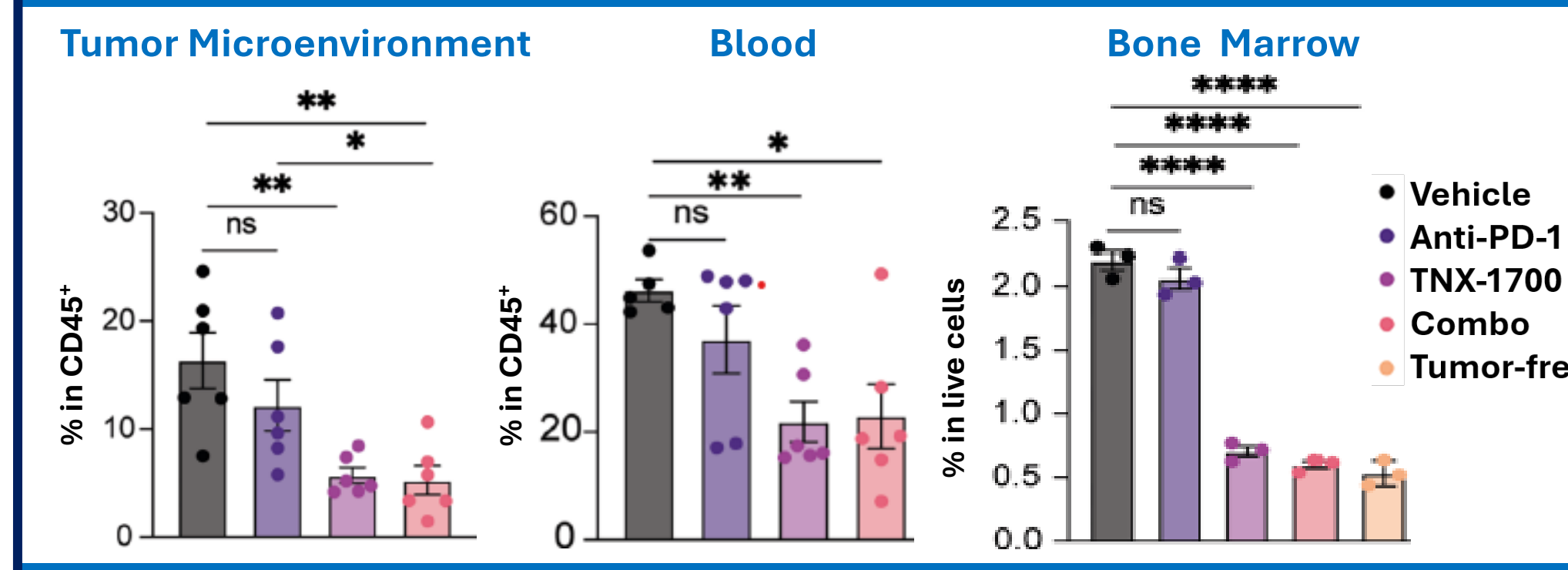
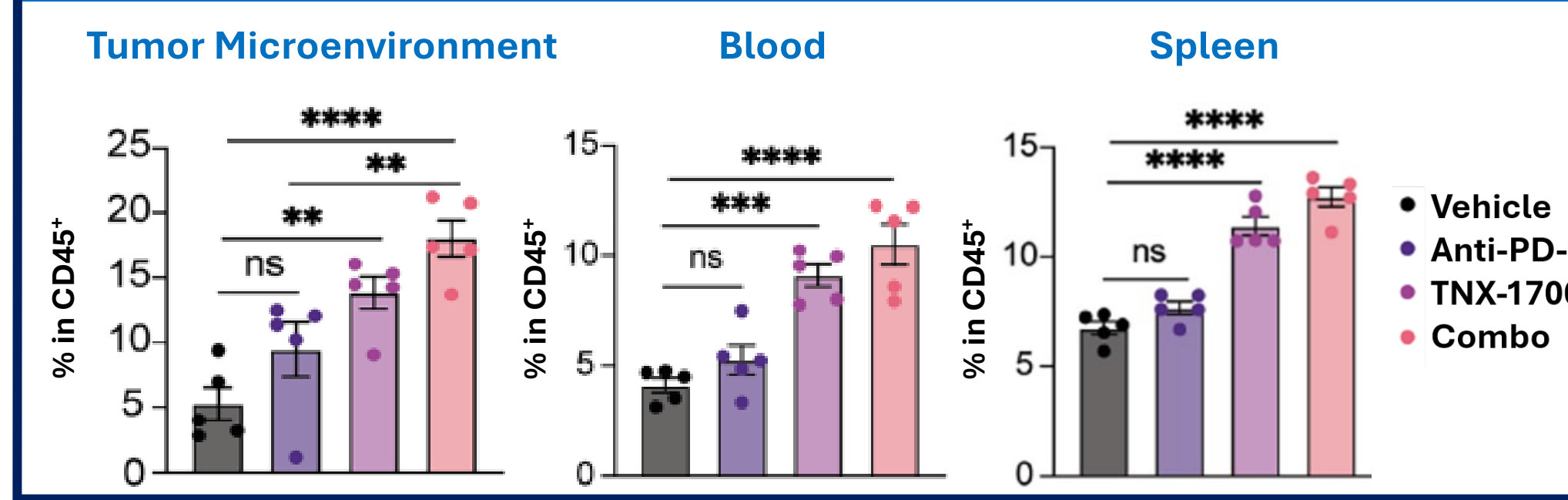


Figure 10. TNX-1700 Increases CD8+ T-Cell Infiltration



Summary of Efficacy

Model	Anti-PD-1	TNX-1700	TNX-1700 + Anti-PD-1
ACKP s.c. GC	-	-	+++
ACKP Orthotopic GC	++	+	+++
Autochthonous GC	-	++	+++
PC s.c. GC	+	++	+++
Liver Metastasis	-	++	+++
Lung Metastasis	-	++	+++
ACKP s.c. CXCR4-KO	-	-	-

Conclusions

- TNX-1700 is a first-in-class CXCR4 partial agonist
- TNX-1700 normalizes cancer-driven myelopoiesis and reduces PMN-MDSCs
- TNX-1700 exhibits single agent efficacy, restores anti-tumor immunity and enhances anti-PD-1 therapy
- TFF2 reduction correlates with elevated PMN-MDSC in GC
- These findings represent a novel strategy to overcome checkpoint resistance and support clinical development in gastric cancer

References

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