

Characterizing micvotabart pelidotin's (MICVO's) anti-tumor, immunostimulatory, and synergistic activity in immunotherapy sensitive and refractory tumor models

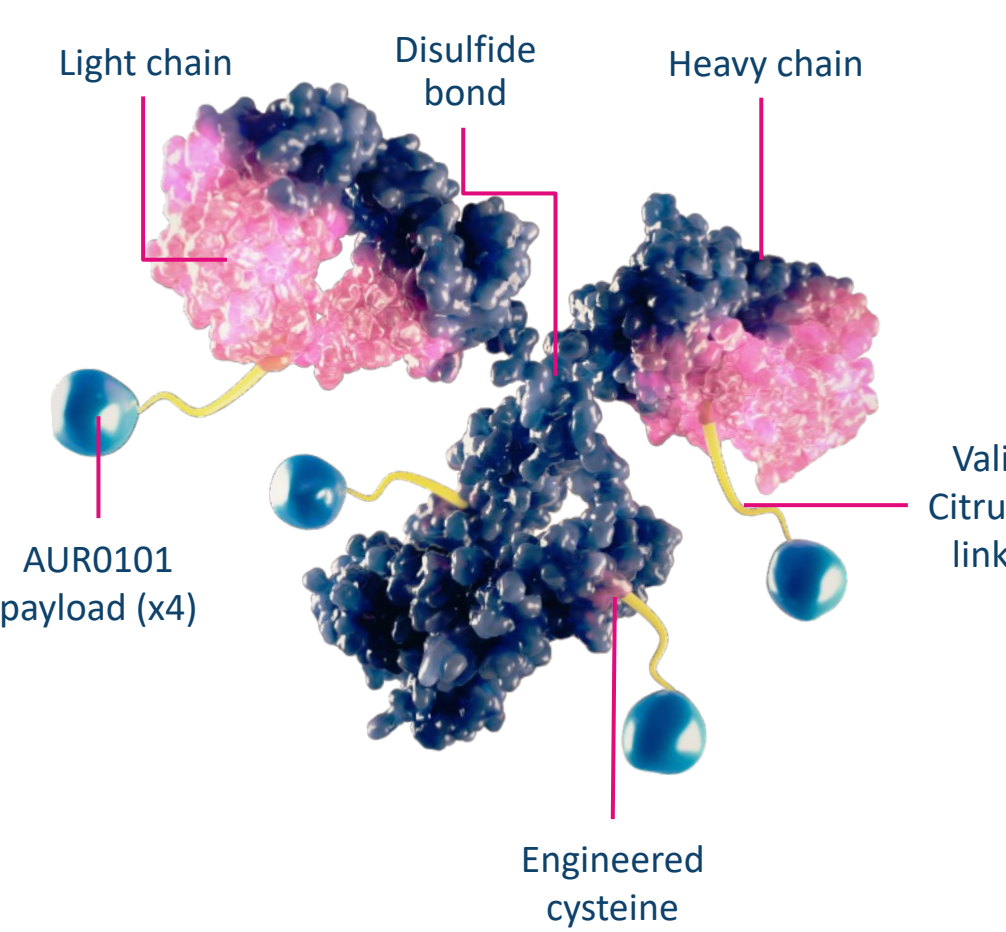
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MICVO is the First ADC with a Target in the Tumor Extracellular Matrix (ECM), Not on the Cell Surface

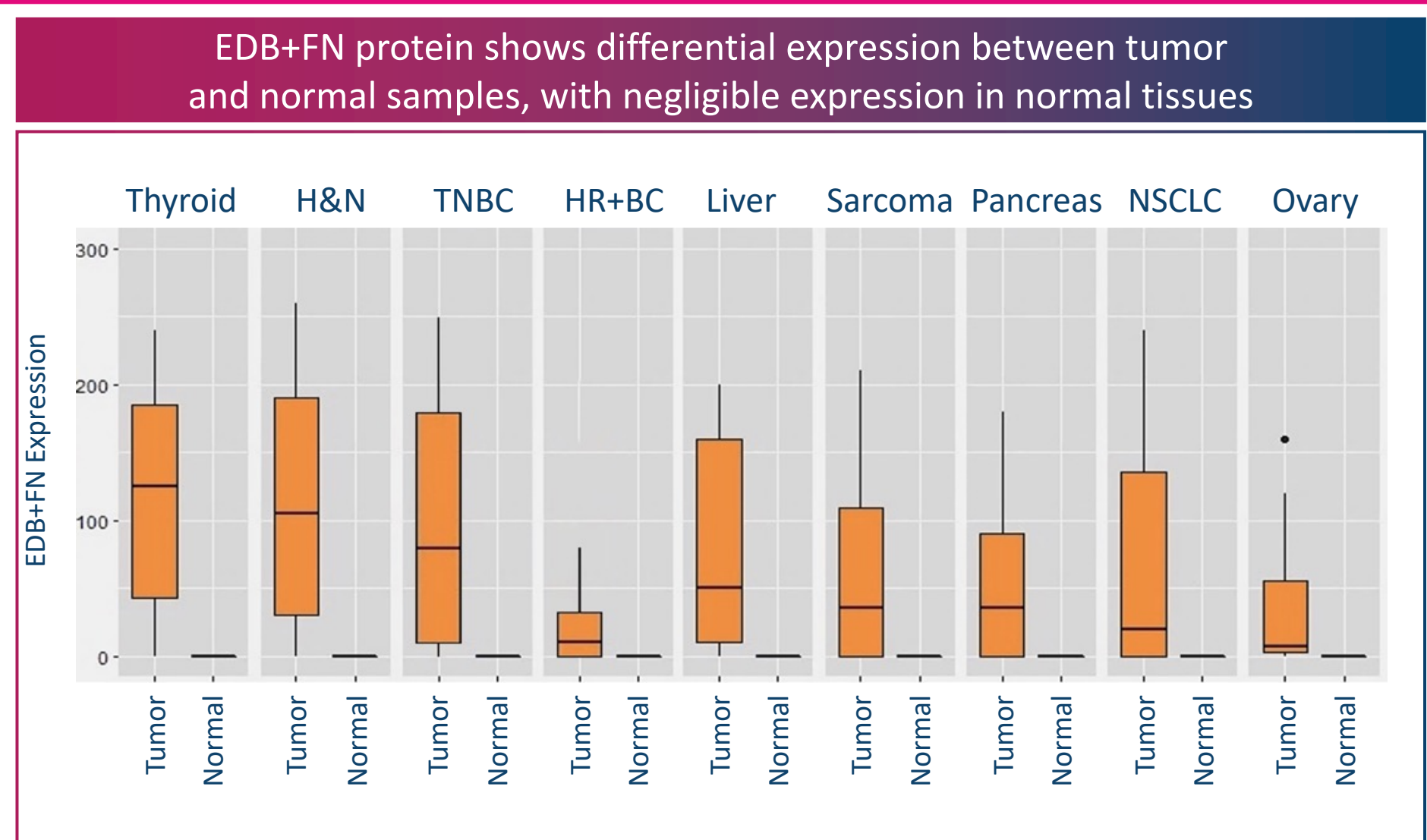


Key Potential Advantages

PURPOSE-BUILT	- Structural integrity with high avidity-driven binding Site-specific, extracellular cleavable Valine Citrulline linkers
PREDICTABLE	Uniform DAR* of 4 provides improved therapeutic window Reduced free payload in serum, C_{max} ~4 days post administration
POTENT	- Four optimized auristatin 0101 microtubule directed payloads - Maximize broad tumor-killing and biological potency
PERMEABLE	- Optimized membrane diffusion to enable bystander killing Fast payload clearance to reduce off-target effects

- MICVO is composed of a monoclonal antibody targeting EDB+FN, an optimized auristatin 0101 payload, and a site-specific protease-cleavable linker.
- A mouse analog of MICVO (maMICVO) was used for in-vivo studies in syngeneic tumor models, retaining the L19 Fab region and auristatin 0101 payload at a near drug-to-antibody ratio of four, with a mouse IgG2a isotype and stochastic conjugation replacing the human IgG1 isotype and site-specific conjugation.

EDB+FN is Expressed in the ECM of Many Solid Tumors

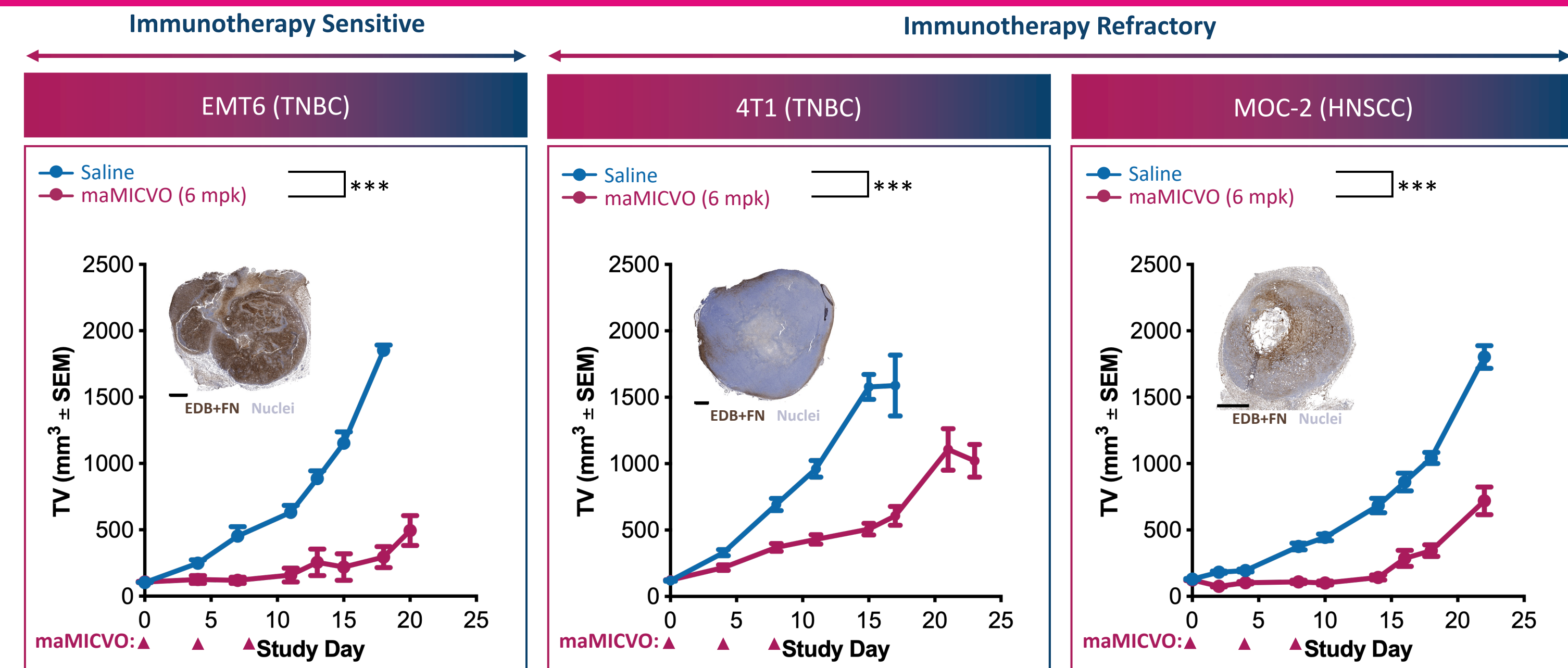


Key biological drivers of response in addition to EDB+FN expression

- Binding of MICVO to EDB+FN
- Presence of extracellular proteases (cathepsins)
- Low pH to enable cathepsin proteolytic activity
- Stromal architecture (e.g., spatial orientation of ECM fibers)
- Immunogenic tumor microenvironment (TME)

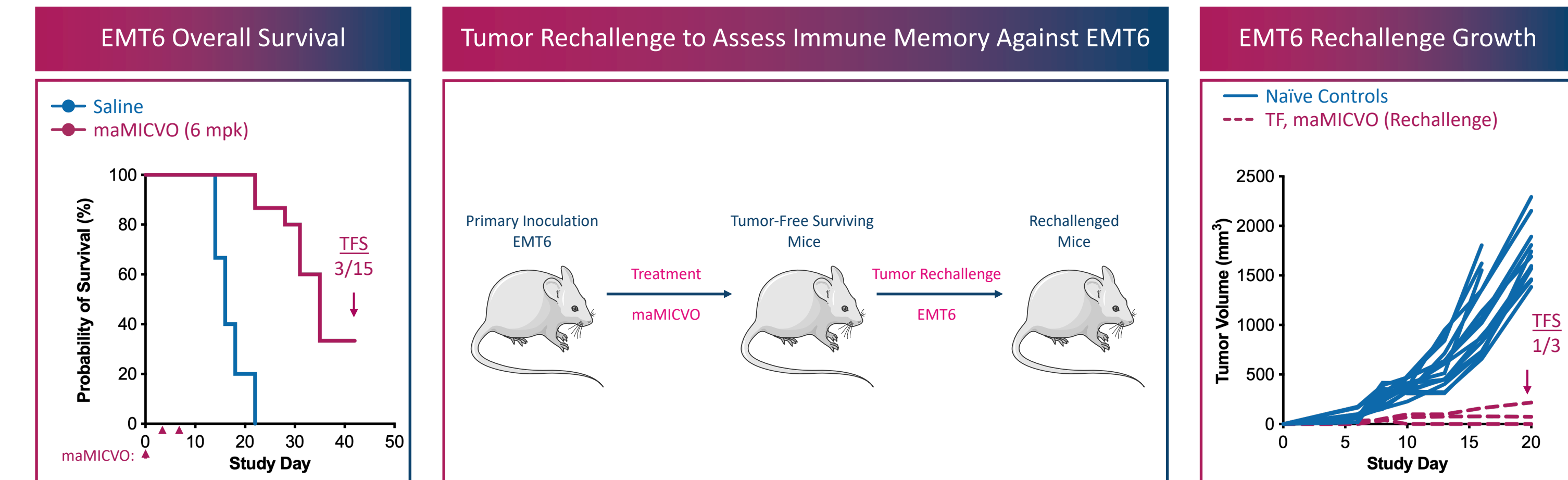
Recent translational findings identify factors beyond EDB+FN expression that drive MICVO response. PYXS developed an exploratory IHC assay to characterize EDB+FN expression and localization (9). Several studies identified additional biological drivers that may confer sensitivity to MICVO across multiple solid tumor types.

maMICVO Shows Anti-Tumor Activity in Immunotherapy Sensitive and Refractory Syngeneic Tumor Models



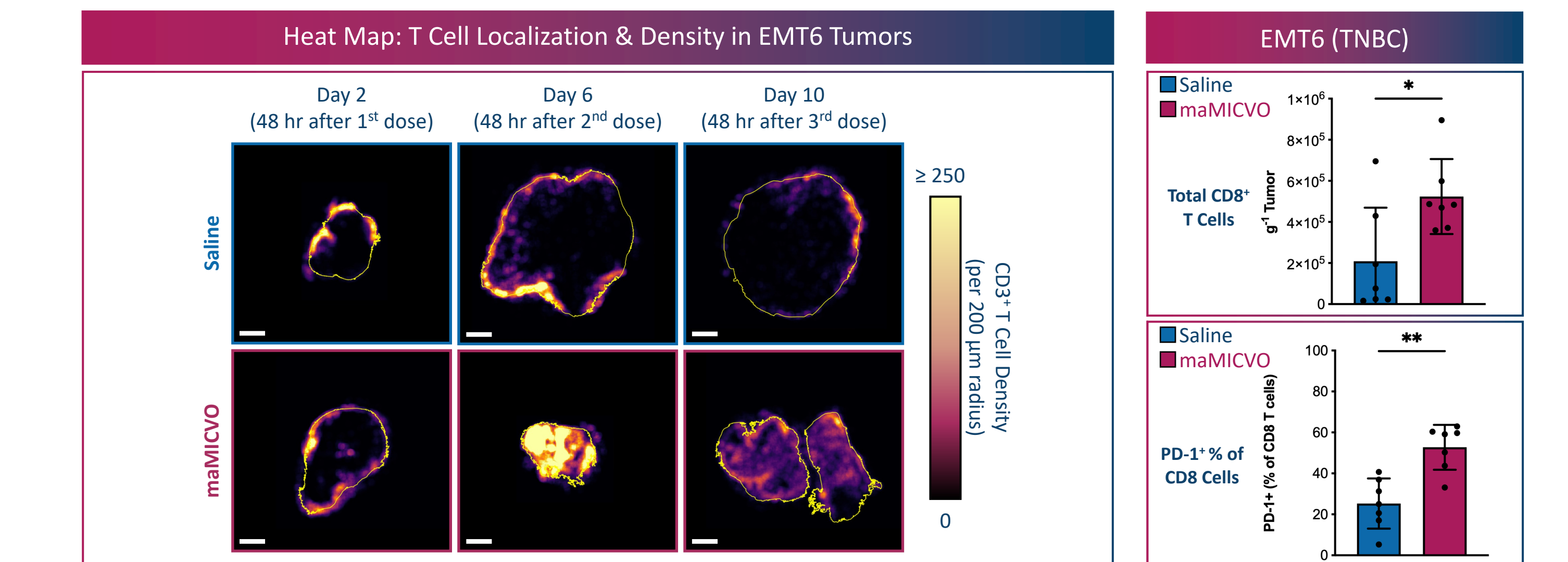
maMICVO showed anti-tumor activity in syngeneic tumor models regardless of immunotherapy sensitivity or EDB+FN expression (6,8,10). EMT6, 4T1, and MOC2 tumor-bearing mice were treated with saline or maMICVO (6 mg/kg, Q4Dx3). All treatments were well tolerated, with no significant body weight loss. P values were determined by unpaired two-tailed Welch's t-test on log10-transformed tumor volumes with Holm-Sidak correction across measurement days: ***P ≤ 0.001.

maMICVO Elicits Potent Immune Memory that Prevents Tumor Recurrence



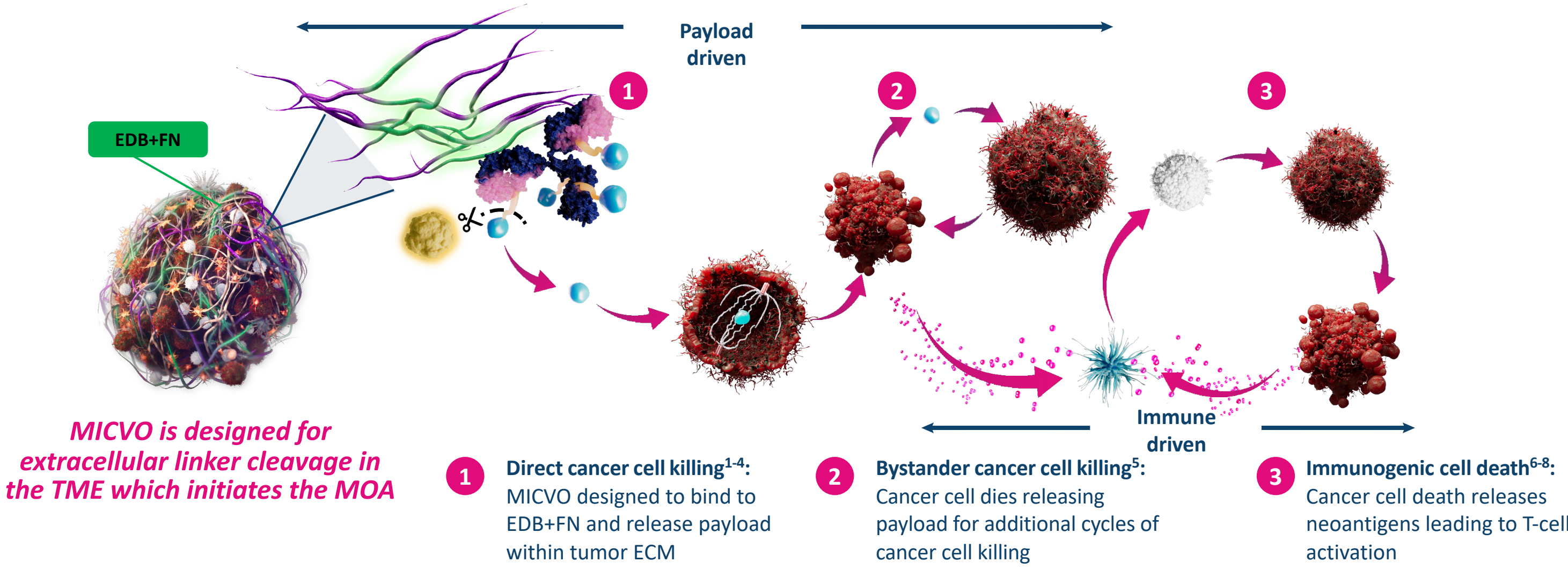
maMICVO elicits potent immune memory that prevents tumor recurrence (6). For the rechallenge experiment, mice that achieved complete regression following maMICVO monotherapy (n=3) were re-inoculated with EMT6, and tumor growth was monitored.

maMICVO Converts T Cell-Excluded Cold Tumors Into Immune-Infiltrated Hot Tumors in the Immunotherapy Sensitive EMT6 Model

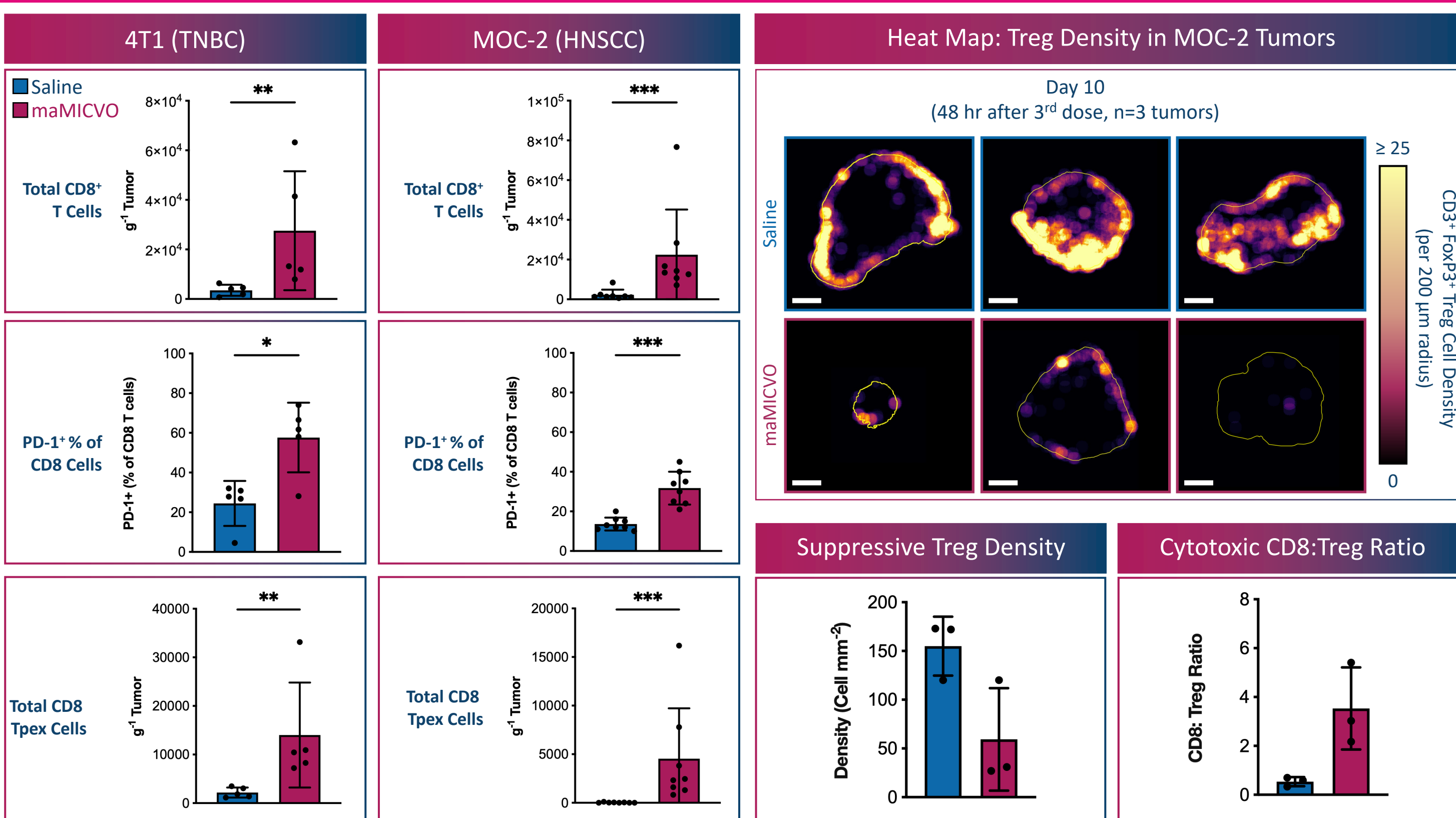


maMICVO induces T cell infiltration into tumors (6). EMT6 tumors from saline- or maMICVO-treated mice (6 mg/kg, Q4Dx3) were collected 48 hours after dosing and processed for mIF to quantify the density and distribution of CD3 T cells by QuPath. Heat maps showed increased T cell density within tumors in maMICVO-treated mice relative to saline controls. Data are from one experiment (n = 3 per group). Flow cytometry analysis of EMT6 tumor suspensions showed increased numbers of CD8 T cells and PD1+ CD8 T cells at Days 10 post-maMICVO. Data are from two independent experiments (n = 7 per group). P values determined by Mann-Whitney U-test: ns, P > 0.05; *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001.

MICVO Delivers Potent Anti-Tumor Activity Through a Three-Pronged Mechanism of Action (MOA)

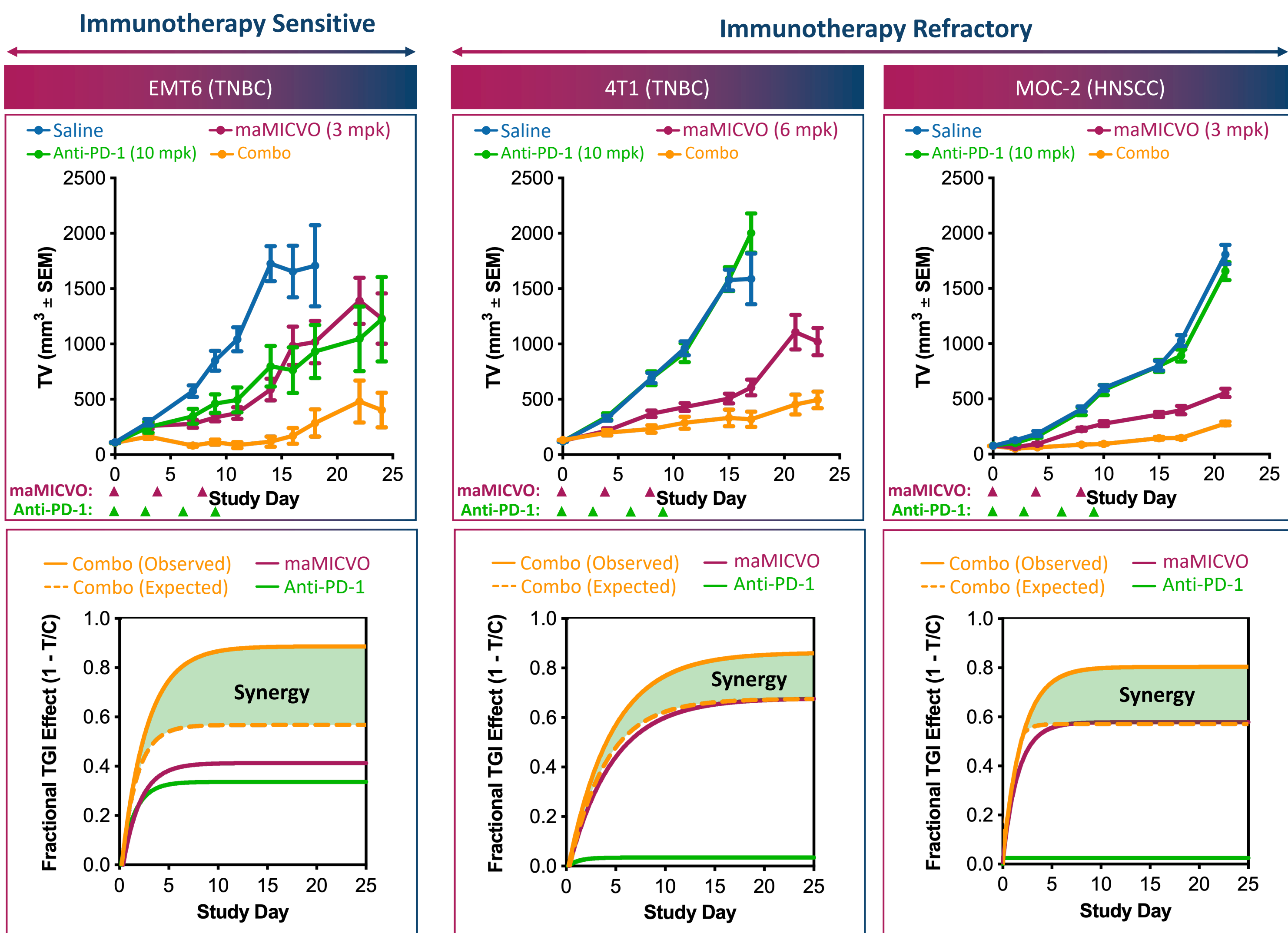


maMICVO Modulates the Tumor-Immune Microenvironment in Immunotherapy Refractory Syngeneic Tumor Models



maMICVO reduced intratumoral Treg burden, promoting a more immune-permissive microenvironment in MOC2 tumors (10). Flow cytometry analysis of 4T1 and MOC2 tumor suspensions showed increased numbers of CD8 T cells and PD1+ CD8 T cells at Days 10 post-maMICVO. Data are from two independent experiments (n = 4-8 per group). MOC2 tumors from saline- or maMICVO-treated mice were collected 48 hours after the third dose and processed for mIF to quantify the density and distribution of CD8 T cells (CD3+ CD8+), CD4 T cells (CD3+ CD8-), and Tregs (CD3+ FoxP3+) by QuPath. Representative heat maps showed reduced Treg burden in maMICVO-treated tumors relative to saline controls. QuPath analysis showed unchanged CD4 T cell density, but trends toward reduced Treg density and lower Treg-to-CD4 frequency, accompanied by higher CD8:Treg ratios. Data are representative of a single experiment (n = 3 per group). P values determined by Mann-Whitney U-test: ns, P > 0.05; *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001.

maMICVO Sensitized Immunotherapy Refractory Tumors to Anti-PD-1 and Demonstrated Synergistic Anti-tumor Activity



maMICVO combined with anti-PD-1 produced greater anti-tumor efficacy than either treatment alone (6,8,10). EMT6, 4T1, and MOC2 tumor-bearing mice were treated with saline, maMICVO, mouse anti-PD-1, or the combination. All treatments were well tolerated, with no significant body weight loss (10). As expected, mouse anti-PD-1 monotherapy had minimal effect on 4T1 and MOC2 tumor outgrowth, whereas maMICVO monotherapy delayed tumor growth across syngeneic tumor models. This effect was further enhanced by combining maMICVO with anti-PD-1, resulting in greater anti-tumor activity than either monotherapy alone. Bliss independence analysis confirmed synergy between maMICVO and anti-PD-1.

Conclusion

- MICVO is a first-in-concept ADC whose tumor specific extracellular targeting strategy and intentional antibody/linker/payload design distinguishes it from conventional ADCs by enabling efficient payload delivery across diverse tumor types, regardless of cancer cell internalization or antigen density.
- maMICVO exerts direct anti-tumor activity while actively modulating the tumor-immune microenvironment.
- This remodeling is driven by increased T cell infiltration, a higher CD8-to-Treg ratio, and the induction of Tpx cells within tumors.
- Together, these effects enable maMICVO to synergize with anti-PD-1, driving deeper anti-tumor responses across both immunotherapy sensitive and refractory tumor models.
- These data support the on-going clinical evaluation of MICVO as a monotherapy (NCT05720117) and in combination with pembrolizumab (NCT06795412) in patients with difficult-to-treat cancers, including recurrent/metastatic head and neck squamous cell carcinoma.

References: (1) Hooper A et al., Mol Cancer Ther (2022). (2) Maderna A et al., J Med Chem (2014). (3) Shen C et al., Mol Cancer Ther (2025). (4) Facklam A et al., Cancer Res (2025). (5) Severe N et al., Cancer Res (2024). (6) Rodriguez et al., Cancer Res (2025). (7) Iovino M et al., Mol Cancer Ther (2025). (8) Rodriguez et al., Mol Cancer Ther (2025). (9) Lewandowski, SL et al., Lab. Invest. A Jour. of Tech. Meth. and Path (2026). (10) Rodriguez et al., Cancer Res (2026)