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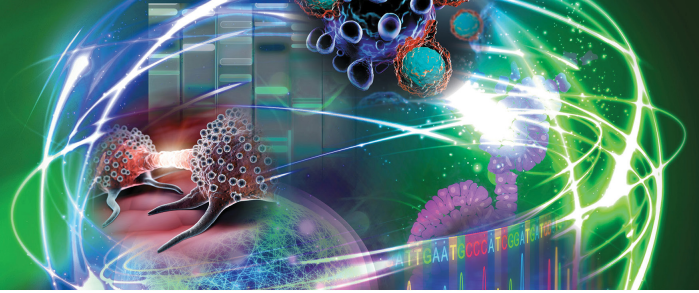
ANNUAL MEETING 2021
VIRTUAL ★ #AACR21
APRIL 10-15, 2021 AND MAY 17-21, 2021 ★ AACR.ORG ★ AACR.ORG/AACR2021



Chimeric antigen receptor macrophages (CAR-M) induce antitumor immunity and synergize with T cell checkpoint inhibitors in pre-clinical solid tumor models

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Disclosure Information

I have the following financial relationships to disclose.
Employee of:

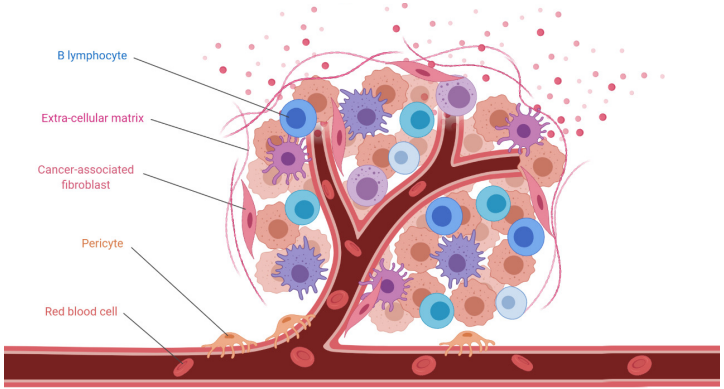
Carisma Therapeutics Inc.

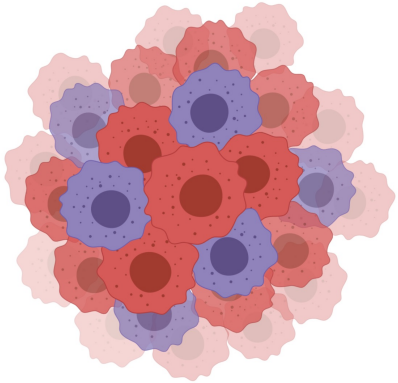
Solid tumor challenges for adoptive cell therapy

1. **Trafficking & penetration**
   - Extravasation
   - Homing
   - Penetration

2. **Tumor microenvironment**
   - Immunosuppression
   - Exhaustion
   - Metabolic challenges
   - Poor proliferation & persistence
   - Low antigen presentation
   - Low Th1 cytokines

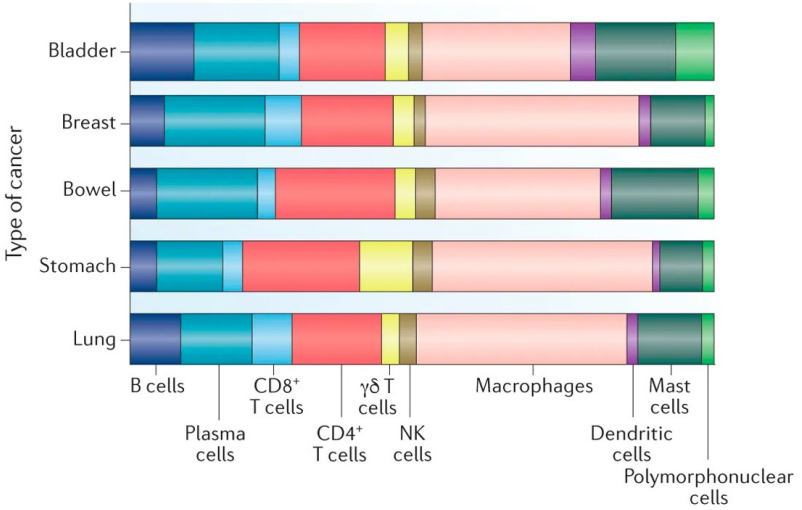
3. **Target antigen heterogeneity**
   - Inherent resistance
   - Antigen negative relapse





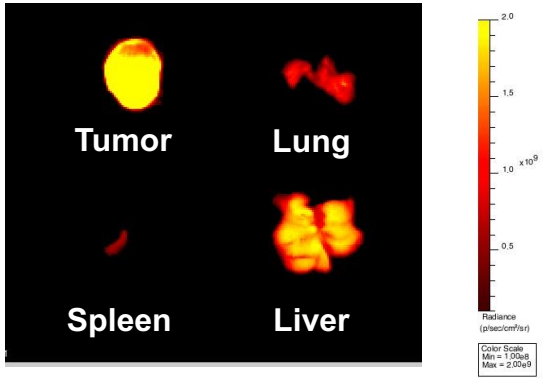
Monocytes & macrophages home to tumors

Myeloid cells are abundant in solid tumors



Pollard JW, et al. Nat Rev Drug Discov. 2019.

Adoptively transferred macrophages home to tumors



Biodistribution of IR-labeled human CAR-M (Gastric carcinoma xenograft model)

Klichinsky M. et al. Nature Biotechnology. 2020

Ad5f35 induces CAR expression and promotes an M1 phenotype in murine MACs without affecting viability

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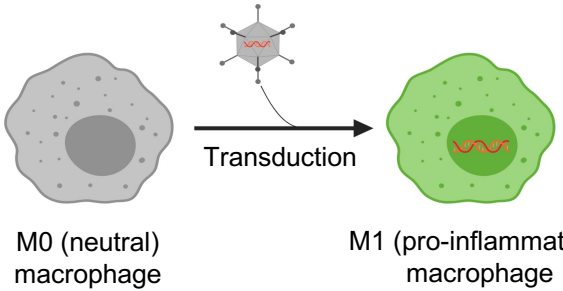
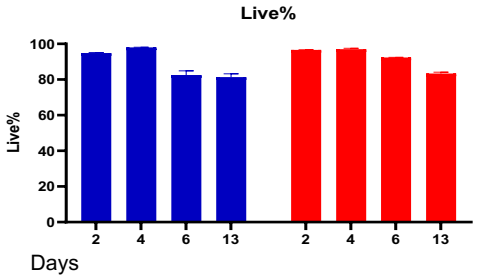
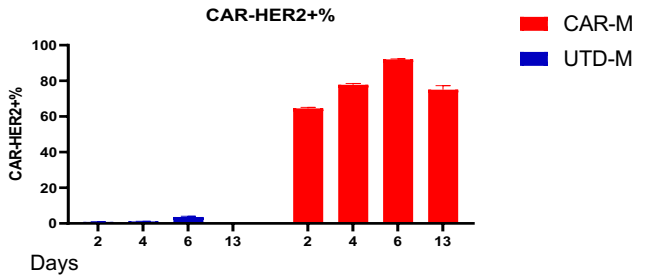
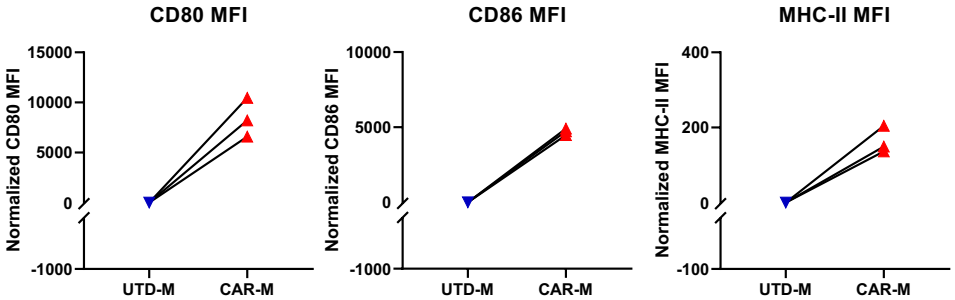


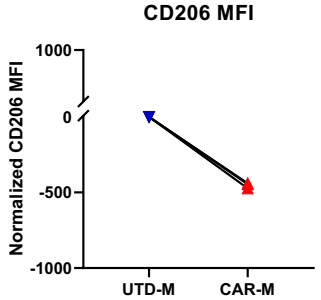




M1 Markers

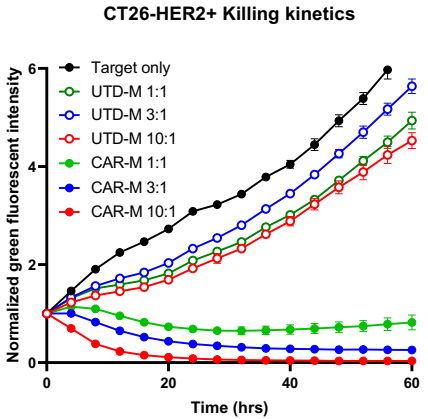


M2 Marker

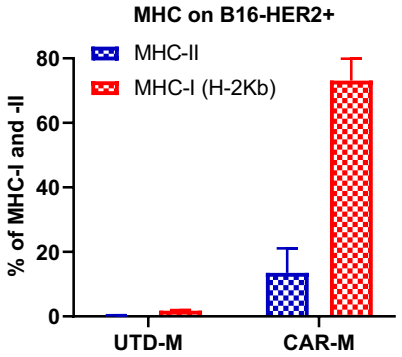


CARs redirect multiple macrophage effector functions

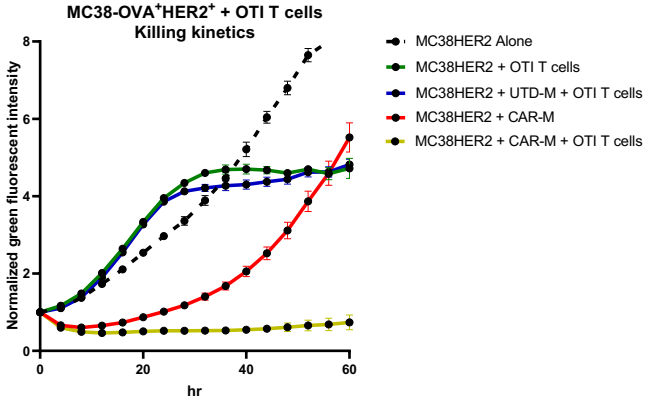
CAR-M clears HER2+ target cells



CAR-M induce MHC expression on tumor cells



CAR-M enhance tumor killing of transgenic TCR T cells (OTI OVA model)



CAR-M shrink tumors and improve overall survival in immunocompetent mouse models

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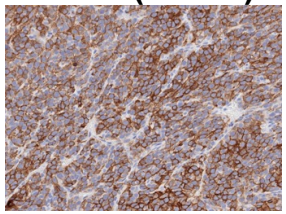
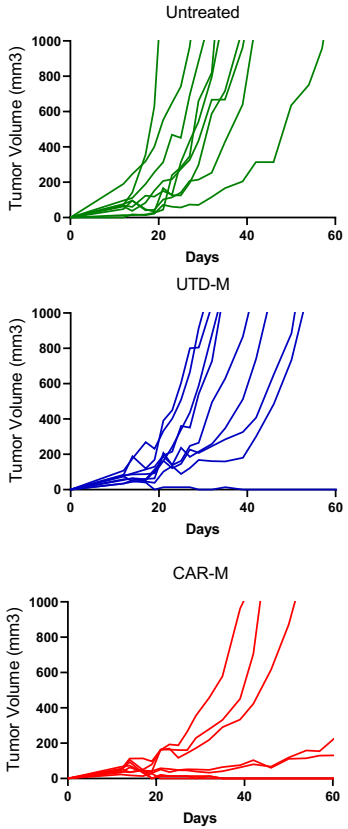
CAR-M lead to tumor control and improve OS against established CT26 (colon cancer) HER2+

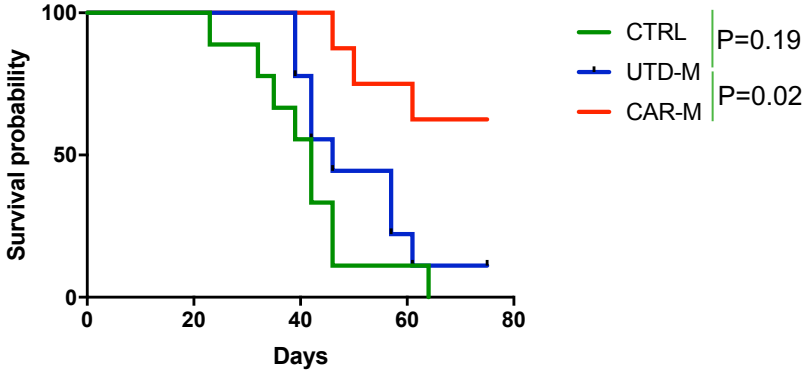
CT26 (HER2)



HER2 IHC: HER2 3+

Tumor	**Subcutaneous, grown 15 days**
Treatment	Local administration





	n	Alive @ Day 75	Median Survival
CTRL	9	0/9 (0%)	42 days
UTD-M	9	1/9 (11.1%)	46 days
CAR-M	8	5/8 (62.5%)	Not reached

UTD: Untransduced; CAR: anti-HER2; OS: overall survival

CAR-M reprogram and activate the TME in immunocompetent pre-clinical models

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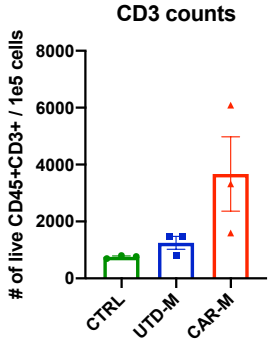
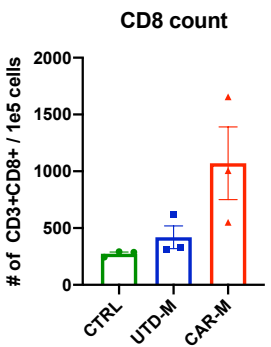
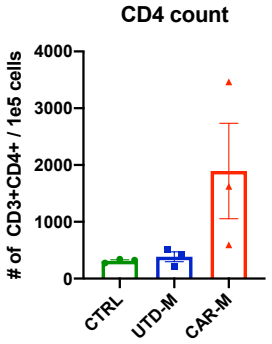
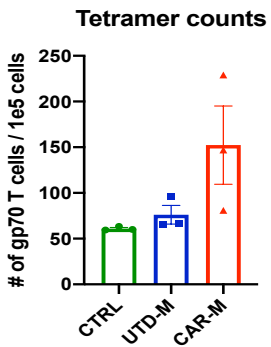
Increased infiltration of T cells

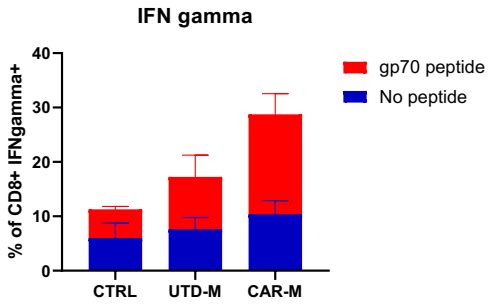


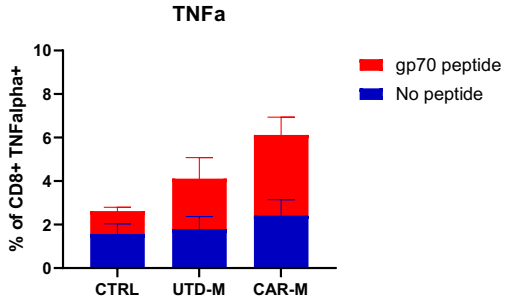




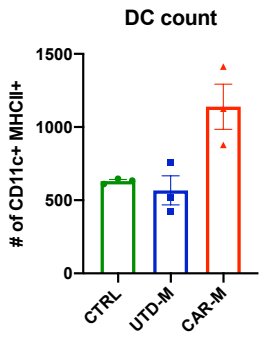


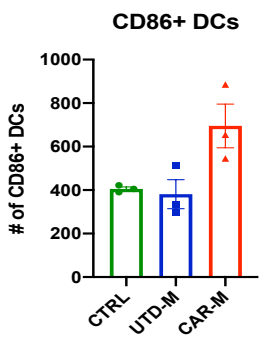
Ex vivo TIL restimulation with gp70



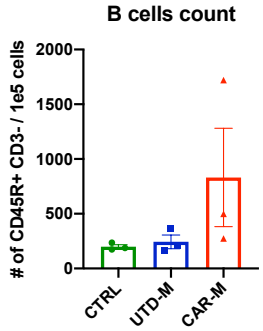


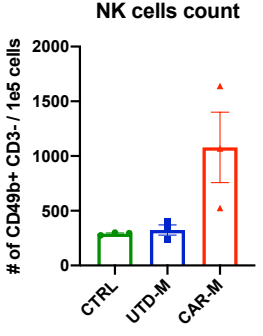
Increased infiltration & activation of DCs



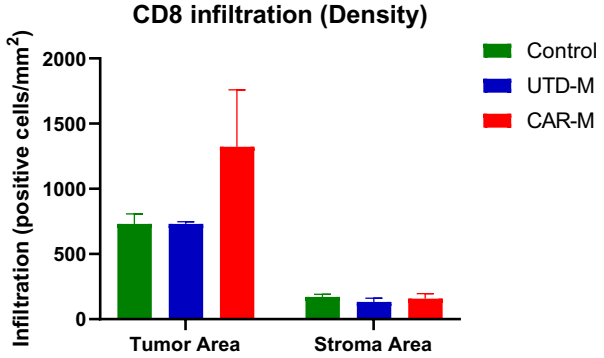


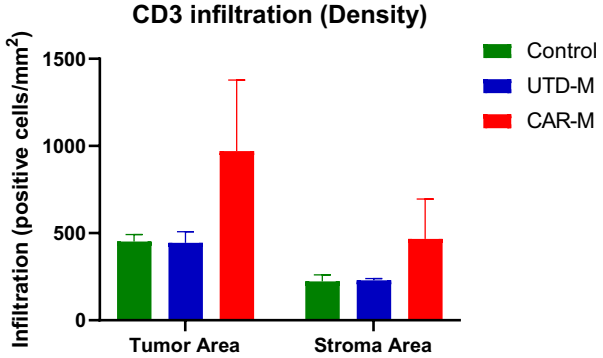
Increased infiltration of B cells and NK cells



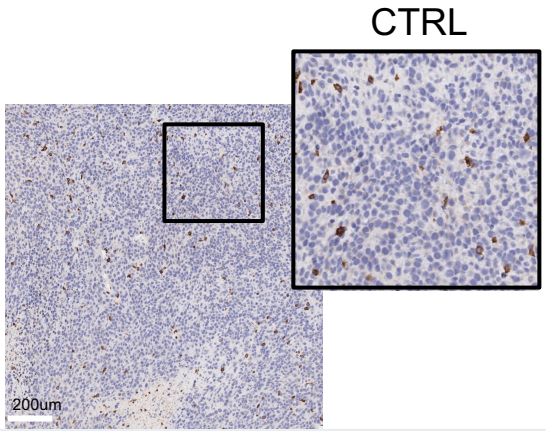


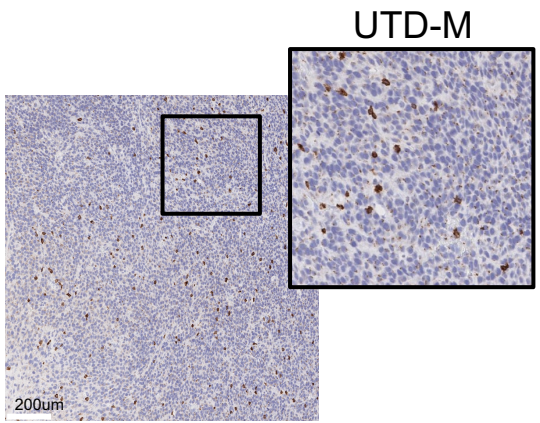
CAR-M drive T cell infiltration into solid tumors

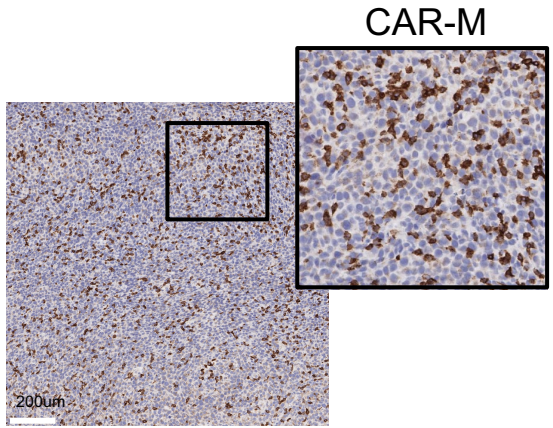




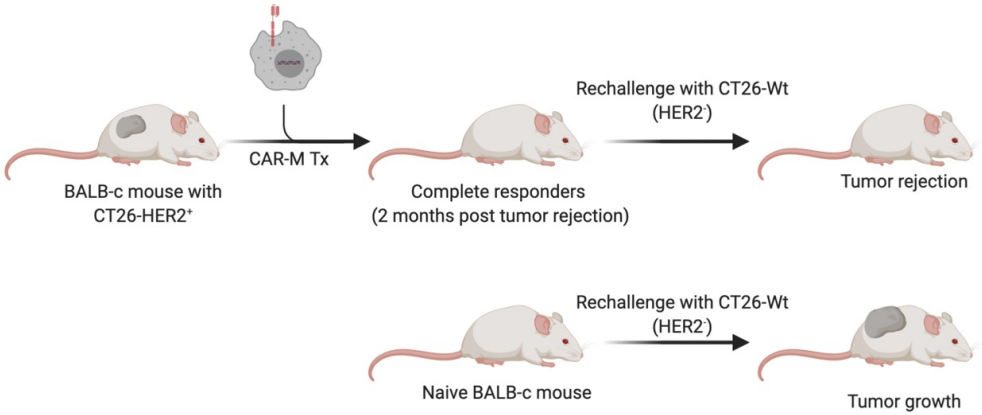
Representative CD8 IHC



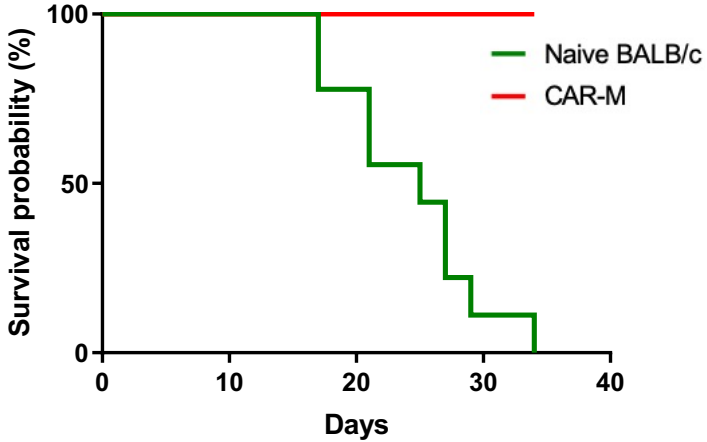




CAR-M therapy vaccinates mice against tumor recurrence and prevents antigen negative relapse



CT26 Wt (HER2-) rechallenge: Kaplan Meir Survival Curve



CAR-M promote systemic anti-tumor response and enhance abscopal effect

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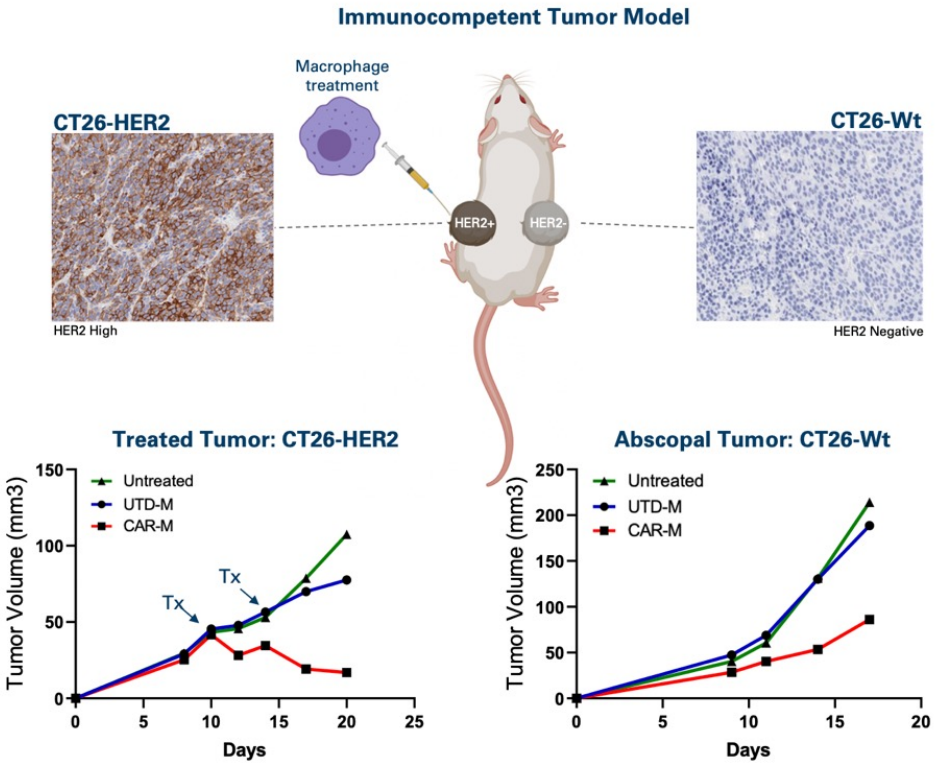
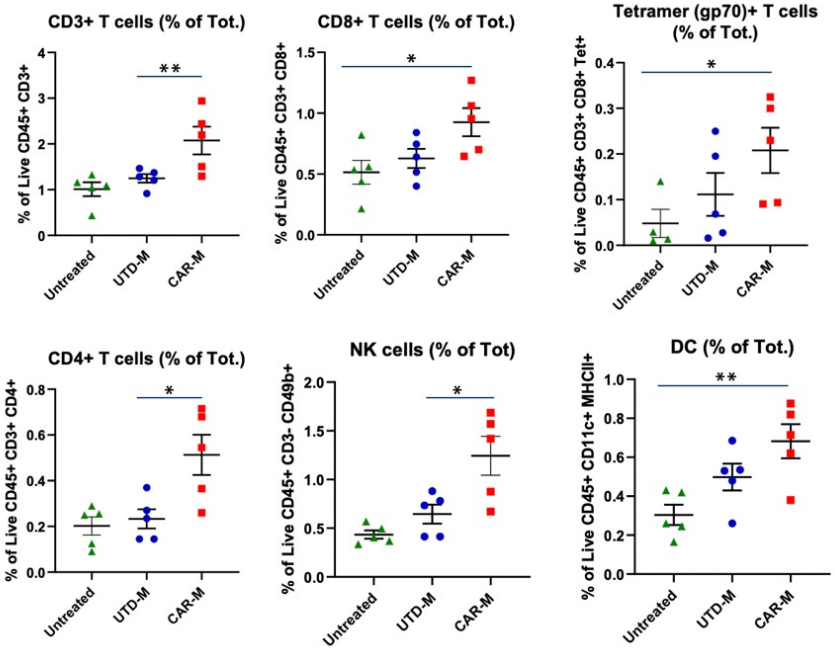
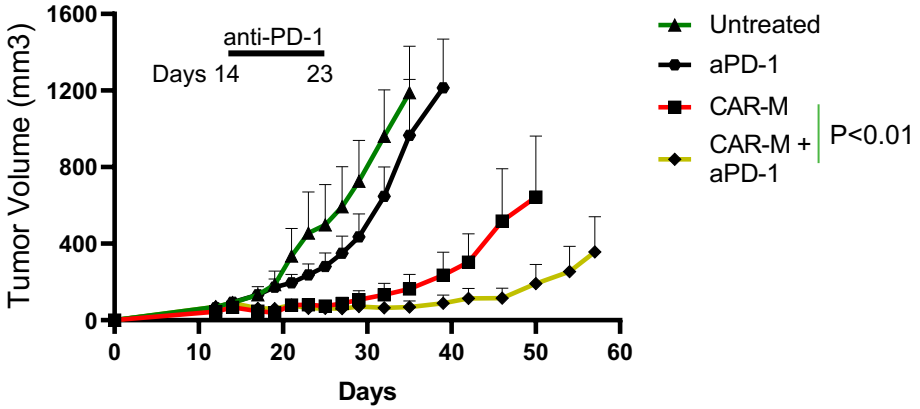
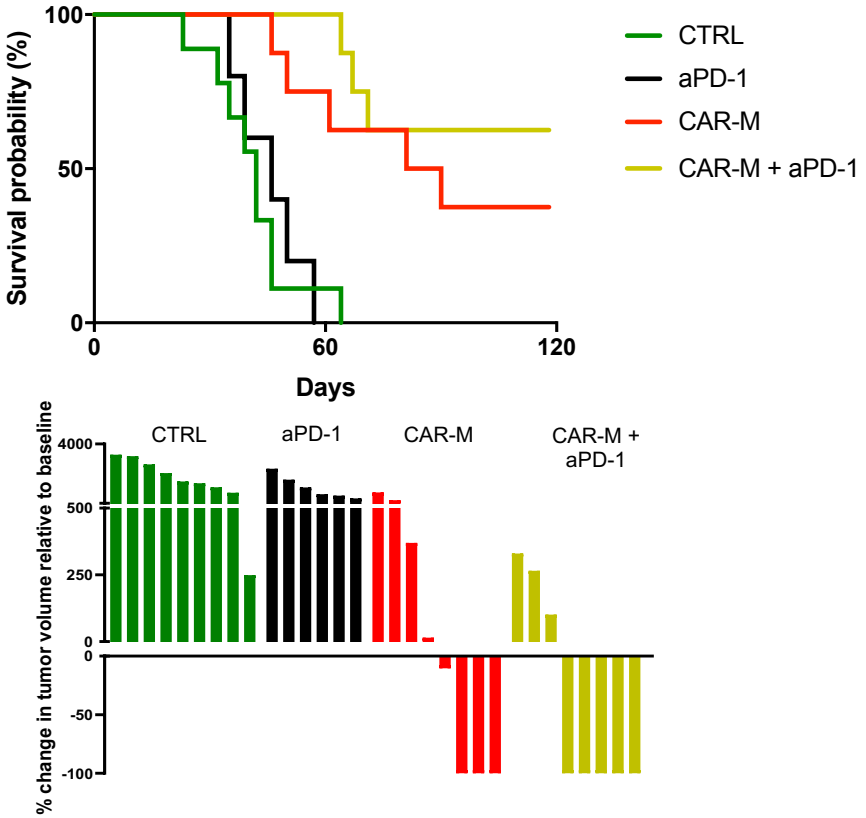


Evaluation of the TME in the HER2- (abscopal) tumor



CAR-M + PD-1 blockade leads to improved tumor control and survival in immunocompetent animals





Conclusions

- CAR-M quickly eradicate tumor cells in a CAR- and HER2-specific way
- CAR-M induce MHC expression on tumor cells and enhance immunorecognition of the target cells by T cells
- Local administration of CAR-M modulates the TME, impacts primary and abscopal tumor growth and increases mice survival
- CAR-M therapy vaccinates mice against tumor recurrence and prevents antigen negative relapse
- The combination of CAR-M with anti-PD-1 blockade leads to synergistic tumor control and significantly increases overall survival