Background Poor prognosis for patients with metastatic castration resistant prostate cancer (mCRPC) has inspired efforts to develop effective treatments for advanced disease. Our lab has developed a chimeric antigen receptor (CAR)-engineered T cell targeting prostate stem cell antigen (PSCA), which is overexpressed in a majority of primary and metastatic prostate cancers. We believe PSCA-CAR T cells will provide a safe and effective strategy for improving clinical outcomes for mCRPC patients. While encouraged by clinical activity in our phase 1 trial (NCT03873805), the immunosuppressive tumor microenvironment (TME) will limit therapeutic potential. Central to tumor/immune cell interactions is the transcription factor, signal transduction and activation of transcription-3 (STAT3), recognized for its critical role in regulating multiple tumor-associated myeloid cell-related genes known to suppress anti-tumor immunity, including type-I IFNs, IL-10, IL-12, TGFβ, and PD-L1. Thus, we hypothesized that TME modulation with a TLR9-guided STAT3 anti-sense oligonucleotide CpG-STAT3ASO (CSI3) would provide myeloid cell-selective STAT3 inhibition, which combined with PSCA-CAR T cells will improve responses in mCRPC.

Methods Using a PSCA knock-in (hPSCA-KI) immunocompetent mouse model of prostate cancer (Murad et al., 2021 Mol Ther), we describe cyclophosphamide (Cy) preconditioning as crucial for unleashing the therapeutic potential of PSCA-CAR T cells, yet still achieving approximately 50% curative responses. Here, we interrogated synergy of Cy and PSCA-CAR T cells combined with targeted STAT3 inhibition with CSI3. Following dosing optimization, tumor reduction and survival kinetics in subcutaneous or intratibial prostate tumors were assessed. Modulation to tumor and systemic immune landscapes using CSI3 treatment was assessed via flow cytometry, Nanostring digital spatial profiling, and immunohistochemistry.

Results In an intratibial bone metastatic prostate cancer model, Cy and CAR T cell treatment was effective in curing 50% of mice. Impressively, we demonstrated 88% curative response rate when combined with CSI3 treatment. The benefit in survival via CSI3 necessitated Cy preconditioning, as only 25% of mice were cured when treated with the CAR T cell/CSI3 combination alone. Lastly, no cures were seen in single treated mice. Analysis is on-going to determine changes in the immune landscape when treated with Cy, PSCA-CAR T cells, and CSI3 combinations.

Conclusions Alone, PSCA-CAR T cell or CSI3 targeted approaches are insufficient in producing a robust immune response without dose limiting toxicities. Our data suggests that myeloid cell-selective STAT3 inhibition in combination with our PSCA-CAR T cells may synergize to improve overall responses and boost endogenous anti-tumor immunity. In sum, this approach presents an exciting avenue for clinical development in mCRPC.