

Title

"¹⁷⁷Lu-PSMA-617 Molecularly Targeted Radionuclide Therapy Increases the Efficacy of B7-H3 Targeted CAR T-cell Therapy in Prostate Cancer"

Authors

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Background

The introduction of ¹⁷⁷Lu-PSMA-617 molecularly targeted radiopharmaceutical therapy (MTRT) marked a significant advancement in the treatment of mCRPC. Approximately half of patients exhibit a significant prostate-specific antigen decline of 50% or greater, a prognostic biomarker for improved survival, with many achieving a state of minimal residual disease. However, long-term remissions remain elusive, and disease progression typically occurs in mere months after treatment completion. The dramatic tumor burden reduction in lethal PCa from ¹⁷⁷Lu-PSMA-617 may render these solid tumors more susceptible to chimeric antigen receptor (CAR) T-cell therapy. While CAR T-cells have induced unprecedented remission rates in patients with acute lymphoblastic leukemia, patients with solid tumors show limited efficacy due to impaired T cell trafficking into the tumor microenvironment (TME) and immunosuppressive mechanisms in the TME. Herein, we demonstrate proof-of-concept combination therapy using ¹⁷⁷Lu-PSMA-617 and B7-H3 targeted CAR T-cells in preclinical models. B7-H3 was chosen as a CAR target because it is overexpressed on the bulk of prostate cancer cells across various disease states and has even higher expression on radioresistant prostate cancer stem cells, which are thought to drive disease progression post ¹⁷⁷Lu-PSMA-617 treatment completion. By specifically targeting this radioresistant population after initial tumor debulking with ¹⁷⁷Lu-PSMA-617, our strategy addresses a critical mechanism of treatment failure.

Methods

Male NSG mice bearing PC-3 PIP flank tumors were treated with varying doses of ¹⁷⁷Lu-PSMA-617 (0, 200, 400, or 800 µCi). After an additional 12 days, 2 million transduced B7-H3 CAR T-cells or mock T-cells were administered to the mice. Flow cytometry was also performed on tumors and spleens 10 days post T-cell administration.

Results

The combination of ¹⁷⁷Lu-PSMA-617 (400 µCi) and B7-H3 CAR T-cells (2 million) significantly improved survival compared to either treatment alone, with hazard ratios of 4.98 ($p = 0.02$) versus ¹⁷⁷Lu-PSMA-617 alone and 4.46 ($p = 0.03$) versus B7-H3 CAR-T alone (log-rank test). Additionally, complete tumor responses increased in a dose dependent manner with regards to ¹⁷⁷Lu-PSMA-617, as 0%, 25%, 57%, and 83% of mice pre-treated with 0, 200, 400, and 800 µCi before B7-H3 CAR T-cell therapy experienced complete responses, respectively. Furthermore, flow cytometry of tumor infiltrated CARs demonstrated pre-treatment with ¹⁷⁷Lu-PSMA-617 increased the number of CAR T-cells in the tumor, increased the proportion of CD8+ T-cells, and decreased the expression of T-cell exhaustion markers. Lastly, complete responses were higher in ¹⁷⁷Lu-PSMA-617 pre-treated tumors when compared to mice with matched

tumor volumes, suggesting the benefit of ^{177}Lu -PSMA-617 pre-treatment extends beyond tumor burden reduction and may involve favorable microenvironment modulation.

Conclusions

Pre-treatment with ^{177}Lu -PSMA-617 increased the efficacy of B7-H3 CAR T-cell therapy with higher tumor engraftment and lower expression of exhaustion markers.

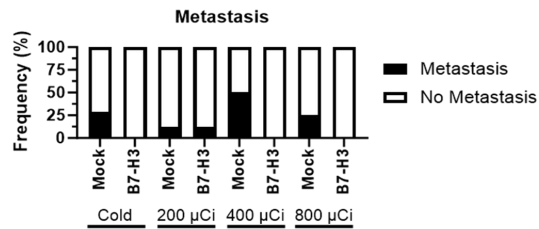
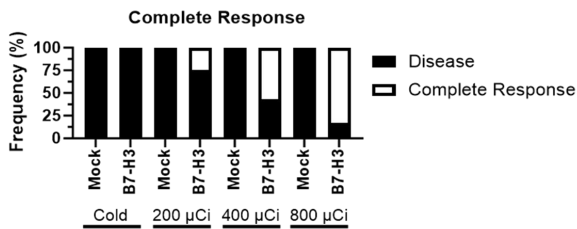
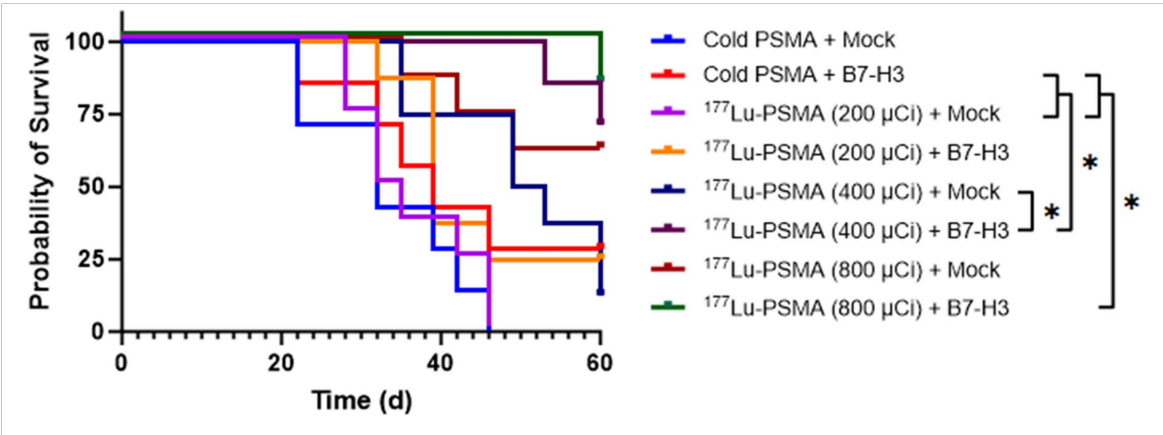
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Conflicts of Interest Disclosure Statement

None.

Survival



Flow Cytometry of B7-H3 CAR vs. ^{177}Lu -PSMA-617 + B7-H3 CAR

