

Combining Radiopharmaceutical Ligand Therapy with CAR T Cells to Overcome the Heterogeneous, Immunosuppressive Prostate Tumor Microenvironment

Authors/Affiliations

Jiangyue Liu^{1,2}, John P. Murad², Iveta Fajnorova³, Yuwei Ren², Kofi Poku⁴, Shuai Yang³, Yu-Hsuan Fu⁵, Cari Young⁴, Lupita S. Lopez², Reginaldo Rosa², Pauline Jeanjean⁷, Ines Azrou³, Ava Fakharpour³, Lea Christian⁴, Yukiko Yamaguchi², Laura H. Porter⁷, Vikram Adhikarla⁵, Russell C. Rockne⁵, Stephen J. Forman, MD⁵, Yun Rose Li, MD⁵, Tanya Dorff, MD⁵, Gail P. Risbridger⁸, Renea Taylor⁸, Christine Mona³, and Saul J. Priceman²

¹ University of Southern California, Los Angeles, CA, United States; ² Keck School of Medicine of USC, Los Angeles, CA; ³ UCLA, Los Angeles, CA; ⁴ Beckman Research Institute of City of Hope, Duarte, CA; ⁵ City of Hope, Duarte, CA; ⁶ Memorial Sloan Kettering Cancer Center, New York, NY; ⁷ Monash Biomedicine Discovery Institute, Clayton, VIC, Australia; ⁸ Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background

¹⁷⁷Lu-PSMA-617 is an FDA-approved targeted radiopharmaceutical therapy (RPT) for metastatic castration-resistant prostate cancer (mCRPC), but durable responses remain limited. While chimeric antigen receptor (CAR) T cell therapy has transformed the treatment of hematologic malignancies, its efficacy in mCRPC is constrained by antigen heterogeneity and an immunosuppressive tumor microenvironment (TME). In a phase 1 clinical trial (NCT03873805) of PSCA-targeted CAR T cells, we observed favorable safety and evidence of activity following cyclophosphamide (Cy) lymphodepletion. Preclinical studies suggest that radiation can enhance CAR T cell efficacy through TME remodeling; however, focal radiation cannot effectively target disseminated metastatic disease. Here, we investigate the combination of systemic ¹⁷⁷Lu-PSMA-617 RPT and PSCA-CAR T cells to overcome immune suppression and tumor heterogeneity in prostate cancer. By leveraging therapies that are FDA-approved or already in clinical development, this strategy offers a clear path toward rapid clinical translation and may provide proof of concept for combining RPT with cellular therapy in immunologically cold tumors.

Methods

Using human PSCA knock-in (hPSCA-KI) syngeneic mouse models, we evaluated the immunomodulatory and therapeutic effects of combining ¹⁷⁷Lu-PSMA-617 RPT, Cy, and PSCA-CAR T cells. Murine prostate cancer cell lines engineered to express human PSMA and/or PSCA were implanted subcutaneously and treated with RPT, Cy, and CAR T cells. Tumors and tumor-draining lymph nodes were analyzed by flow cytometry and single-cell RNA sequencing to characterize immune responses. Tumor growth, survival, body weight, and blood chemistry were monitored to assess efficacy and safety.

Results

We evaluated the efficacy and safety of combining ¹⁷⁷Lu-PSMA-617 RPT with PSCA-CAR T cell therapy in both xenograft and syngeneic prostate cancer models. Integrated flow cytometric and single-cell transcriptomic analyses revealed significant immunologic remodeling following combination treatment. Sequential administration of ¹⁷⁷Lu-PSMA-617 RPT followed by PSCA-CAR T cells improved survival and antitumor responses compared with either therapy alone. Mechanistically, the combination addressed antigen heterogeneity while promoting a more favorable immune microenvironment that supported sustained antitumor activity. Similar findings were observed with ²²⁵Ac-PSMA-617, suggesting broader applicability across radionuclide platforms.

Conclusions

Combining PSMA-targeted RPT with PSCA-CAR T cells enhances antitumor efficacy and durability in preclinical prostate cancer models. The use of clinically relevant therapies supports near-term translational potential. Extension of these findings to ²²⁵Ac-PSMA-617 further highlights the promise of integrating RPT and CAR T cell therapy as a next-generation treatment strategy for mCRPC and other immunologically cold cancers.

Funding Acknowledgements

PCF Young Investigator Award 2021 (PI: Murad); PCF Tactical Award (PI: Priceman); Department of Defense Idea/Expansion Awards (PI: Priceman)

Conflict of Interest Statement

There are no conflicts of interest to report related to the data presented.