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TITLE: Heating Cold Prostate Tumors with PSMA-Targeted Alpha Therapy and Pembrolizumab

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CONTRACTING ORGANIZATION: Joan & Sanford I.Weill Medical College of Cornell University, New York, NY

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14. ABSTRACT

Treatment of prostate cancer using immune checkpoint inhibition combined with androgen receptor signaling inhibitors results is ineffective in most. Other methods of treatment need to be studied to develop novel strategies to improve prognosis of these patients. We hypothesize that the combination of pembrolizumab plus androgen receptor signaling inhibitor plus 225Ac-J591 is safe. We also hypothesize that the addition of 225Ac-J591 to the backbone of pembrolizumab plus androgen receptor signaling inhibitor will lead to more responses compare to pembrolizumab plus androgen receptor signaling inhibitor alone and that we can identify subsets more or less likely to respond. In this project, we will utilize our prospective data and sample sets to: (i) compare the efficacy of the addition of PSMA-targeted alpha emitting radionuclide therapy to anti-PD-1 and AR signaling inhibition versus pembrolizumab and AR signaling inhibition alone; and (ii) assess the optimal patient/tumor population for immune checkpoint inhibition with pembrolizumab with or without PSMA-targeted alpha emitting radionuclide therapy. This project will evaluate whether the combination of PSMA-based targeted radionuclide therapy using alpha emitting 225Ac with immune checkpoint inhibitor and androgen receptor signaling inhibitor will result in more accurate cancer cell targeting and more robust, systemic immune response to maximize their effects. The findings from this project may provide valuable information to help with uncovering cures for men with metastatic castration resistant prostate cancer.

15. SUBJECT TERMS
None listed.

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1. INTRODUCTION

BACKGROUND: Immunotherapy is of tremendous interest to both clinicians and patients based upon the possibility of deep, durable responses, but to date is of limited utility in men with advanced prostate cancer. Androgen receptor (AR) signaling inhibitors have significant efficacy for men with PC and interestingly, both pre-clinical and clinical data support the combination of AR signaling and immune checkpoint inhibition. PC is a radiosensitive disease, curing some men and providing palliation for others, including the bone-targeting isotope radium-223 with a survival benefit. There is both pre-clinical and clinical data supporting radiation to stimulate immune responses. Prostate-specific membrane antigen (PSMA) is a target of interest because of its high level of sensitivity and specificity for PC and PSMA-targeted radionuclides are headed towards approval. Of particular interest are PSMA-targeted alpha-emitters, with very high potency and the potential to generate immune response.

HYPOTHESES / OBJECTIVES: We hypothesize that (1) the addition of 225Ac-J591 will increase the durable response proportion to pembrolizumab plus AR signaling inhibitor and (2) that there are clinical and biomarker subsets associated with treatment outcome.

2. KEYWORDS

Prostate Cancer, metastatic castration resistant prostate cancer, PSMA, pembroluzimab, 225Ac-J591

3. ACCOMPLISHMENTS

What were the major goals of the project?

AIMS / STUDY DESIGN
Aim 1: To compare the efficacy of the addition of PSMA-targeted alpha emitting radionuclide therapy to anti-PD-1 and AR signaling inhibition (versus pembrolizumab and AR signaling inhibition alone), we will perform a clinical trial in men with progressive mCRPC. First, an initial safety lead-in will assess the triplet combination of pembrolizumab, an AR signaling inhibitor of physician choice, and 2 different doses of 225Ac-J591 (one with minimal and one with moderate single-agent toxicity). Following determination of the optimal dose, a randomized phase II trial will treat subjects with a fixed dose of pembrolizumab 600 mg every 6 weeks (for up to 2 years) plus a standard AR signaling inhibitor (until progression or intolerance) with or without 225Ac-J591. The primary endpoint of the study will test the hypothesis that the addition of PSMA-targeted alpha emitter increases the response to immuno-hormonal therapy with 90% power. Key secondary clinical endpoints include 1-year progression-free survival, duration of response, and overall survival.

Aim 2: To prospectively assess the optimal patient/tumor population for immune checkpoint inhibition with pembrolizumab with or without PSMA-targeted alpha emitting radionuclide therapy, we will evaluate immune response, genomic biomarkers, and PSMA molecular imaging and will also evaluate patient reported outcomes.

What was accomplished under these goals?

Specific Aim 1:
Major Task 1: Obtain regulatory approval for multicenter study
Subtask 1: We have completed all parts of Subtask 1 during the initial portion of the funding period. The initial protocol was reviewed, amended following discussions with our pharmaceutical partner (Merck), and subsequently approved. The amended version of the protocol was approved by the Genitourinary Disease Management Team, the Meyer Cancer Center Protocol Review and Monitoring Committee, Radiation Safety Committee, and WCM IRB. Following local approval, approval by HRPO and FDA occurred. The protocol has been activated at WCM and BMH (i.e. both milestones have been achieved).
The study start-up process was initiated at CUMC and in negotiations with DFCI.

Major Task 2: Coordinate and train study personnel for clinical trials
Subtask 1: WCM personnel have been fully trained with ongoing training for amendments. A site initiation visit was conducted for BMH personnel and training records have been accordingly amended.
Initial discussions have begun with CUMC, but formal training will await regulatory approval at that site.

Major Task 3: Conduct clinical trial
Subtask 1: Enrollment and analysis of the phase I portion of the study has been completed. Enrollment in the randomized portion of the trial has been activated in August, 2022.

Table for Phase I patient enrollment:

Phase 1 Enrollment to Trial to Date		**12**	
Patients by Age			
20-29	0	30-39	0
40-49	0	50-59	3
60-69	4	70-79	0
80-89	5	90+	0
Total: 12			
Patients by Gender			
Male	12	Female	0
Total: 12			
Patients by Race			
White	11	African American	1
Asian	0	Native Hawaiian or Other Pacific Islander	0
American Indian or Alaska Native	0	Unknown	
Total: 12			

Patients by Ethnicity			
Hispanic	1	Non-Hispanic	11
Unknown			
Patients Who Completed the Study		**1**	
Patients Who Have Dropped Out of the Study		**1**	

Table for all patient enrollment to end of this reporting period:

Enrollment to Trial to Date		**16**	
Patients by Age			
20-29	0	30-39	0
40-49	0	50-59	3
60-69	4	70-79	3
80-89	6	90+	0
Total: 16			
Patients by Gender			
Male	16	Female	0
Total: 16			
Patients by Race			
White	13	African American	2
Asian	0	Native Hawaiian or Other Pacific Islander	0
American Indian or Alaska Native	0	Unknown	1
Total: 16			
Patients by Ethnicity			
Hispanic	2	Non-Hispanic	14
Unknown			
Patients Who Completed the Study		**1**	
Patients Who Have Dropped Out of the Study		**1**	

Subtask 2:
Preliminary results of phase 1 were submitted to the 2022 Society of Urologic Oncology annual meeting, and accepted for poster presentation (December, 2022), with full phase 1 results planned for submission to the 2023 ASCO Genitourinary Cancers Symposium.

Specific Aim 2:
Major Task 4: (Aim 2a) Evaluation of immune response
Subtask 1:

Collection and processing/storage of serum samples is ongoing
Subtask 2:
Collection and processing/storage of markers of immunogenic cell death is ongoing

Subtask 3:
Collection and processing/storage of samples for microbiome is ongoing

Major Task 5: (Aim 2b) Genomic biomarkers
Subtask 1:
Collection of tissue samples is ongoing

Subtask 2:
Collection and processing/storage of plasma is ongoing

Major Task 6: (Aim 2c) Molecular imaging
Baseline and post-treatment PET imaging is ongoing.
Preliminary analysis of pre-treatment PET imaging for the phase 1 portion of the study will be submitted in abstract form to the 2023 ASCO Genitourinary Cancers Symposium.

Major Task 7: (Aim 2d) Patient reported outcomes
Collection of FACT-P, BPI, and EQ-5D-5L questionnaires is ongoing.

What opportunities for training and professional development has the project provided?

A medical oncology fellow participated in the analysis of the phase I portion of the protocol and will present initial results at the 2022 SUO meeting. This trainee is also submitting updated results to the 2023 ASCO GU Cancers Symposium,

How were the results disseminated to communities of interest?

The initial safety results of the phase I portion of the study were submitted in abstract form and accepted for presentation at the 2022 SUO meeting. Updated results describing an inflammatory syndrome that appears to be cytokine-driven will be submitted to the 2023 ASCO GU Symposium.

What do you plan to do during the next reporting period to accomplish the goals?

The study is co-funded by Weill Cornell Medicine and Merck in addition to DoD funds. As stated in the proposal and SOW, we will continue accrual at the WCM and BMH sites. We will proceed with study start up at additional sites within the PCCTC and anticipate accrual before the next annual report.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

The demand for actinium-225 has increased at a higher rate than supply has increased. This is potentially an issue as a vital material for labeling of the study drug. We have anticipated this and now have a standing order with the Department of Energy that is projected to more than cover needs for this study.

Changes that had a significant impact on expenditures

There is an ongoing workforce shortage within the clinical research enterprise at our institution and at other institutions involved in this protocol. This has resulted in some delays in study start up. This has not resulted in any significant impact on expenditures to date, but the duration of the overall study may necessitate a no cost extension.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:
Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals
N/A

Significant changes in use of biohazards and/or select agents
N/A

6. PRODUCTS

- **Publications, conference papers, and presentations**

  Journal publications.
  Nothing to report

  Books or other non-periodical, one-time publications.
  Nothing to report

  Other publications, conference papers and presentations.
  Nothing to report (but will have abstract presentation/publication(s) to report in the next reporting period.

- **Website(s) or other Internet site(s)**
  Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Nothing to report

- **Other Products**
  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Personnel	Role	Person Month	Percent Effort
Scott Tagawa, M.D.	Principal Investigator	1.2	10%
Paraskevi Giannakakou, M.D.	Co-Investigator	0.6	5%
Neil Bander, MD	Co-Investigator	0.36	3%
Karla Ballman Ph.D	Co-Investigator	0.36	3%
Francesca Khani, MD	Co-Investigator	0.6	5%

Joseph Osborne, MD	Co-investigator	0.6	5%
Mahelia Bissassar	Program Specialist	6.0	50%
Charlene Thomas	Statistician	1.8	15%
Angela Tan	Research Nurse	1.2	10%
Matthew Dallos	Co-Investigator	0.6	5.6%

Name: Scott Tagawa, MD
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked:
Contribution to Project: Dr. Tagawa oversees the entire program, including organizing bi-weekly meetings, reviewing enrollment, meeting with WCM data coordinators and administrative staff, developing new protocols, and enrolling patients on studies. He identifies and recruit patients to the protocol and oversees all conduct of the study.

Name: Paraskevi Giannakakou, M.D.
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.6
Contribution to Project: Dr. Giannakakou assists Dr. Tagawa in coordinating and supervising all translational and correlative sciences for all studies.

Name: Neil Bander, MD
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.36
Contribution to Project: Dr. Bander assists Dr. Tagawa in coordinating and supervising bi-weekly meetings, review eligible patients, meeting with relevant staff associated with the projects and developing new protocols.

Name: Karla Ballman, MD
Project Role: Collaborator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.36
Contribution to Project: Dr. Ballman assists with biostatistical design of WCM investigator initiated studies.

Name: Francesca Khani, M.D.
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.6
Contribution to Project: Dr. Khani assists Dr. Tagawa in coordinating and supervising all translational sciences for all studies.

Name: Joseph Osborne, M.D.
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.6
Contribution to Project: Dr. Osborne assists in the administration the investigational products for this clinical protocol.

Name: Mahelia Bissassar
Project Role: Program Specialist
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 6.0
Contribution to Project: Ms. Bissassar reports directly to Dr. Tagawa. She guides clinical protocols through the regulatory approval processes, coordinate participant accrual, and coordinate study activities across sites.

Name: Charlene Thomas
Project Role: Statistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1.8
Contribution to Project: Ms. Thomas assists with biostatistical design of WCM investigator initiated studies.

Name: Angela Tan
Project Role: Research Nurse
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1.2
Contribution to Project:
Assist with recruitment of patients, completion of study procedures, assessment of adverse events

Name: Matthew Dallos
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.36
Contribution to Project: Dr. Dallos served as PI for the Columbia University Medical Center site, served on the study steering committee, and assisted Dr. Tagawa study design.

Name: Mark Stein
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.14
Contribution to Project: Dr. Stein serves as PI for the Columbia University Medical Center site, serves on the study steering committee, and assists Dr. Tagawa in identifying and recruit patients to the protocol.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The PI at the CUMC site has transitioned from Matthew Dallos to Mark Stein.

Scott Tagawa

*Title: Measuring Patient-Reported Outcomes Related to Radiopharmaceuticals for Prostate Cancer

Major Goals: Goal is to create a new patient-reported outcomes measure for patients receiving targeted radionuclide therapy

*Status of Support: Active (New)

Project Number: W81XWH-20-1-0351

Name of PD/PI: Gonzalez, Brian

*Source of Support: DoD

*Primary Place of Performance: Weill Cornell Medicine, NY, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/01/2020-08/31/2023

* Total Award Amount (including Indirect Costs):

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2022	0.36
3. 2023	0.36

Title: Targeted Therapies
Major Goals: 1) Optimize PSMA-targeted therapeutics (including radionuclides, bispecifics, and drugs) 2) Advance PC immunotherapeutics based on pre-clinical investigations 3) Develop new therapies for neuroendocrine / small cell PC 4) Identify effective treatments and biomarkers based on discovery of mechanisms of PC therapy resistance and sensitivity 5) Open PCCTC studies to underrepresented minorities in Brooklyn and Upper Manhattan (incl. VAMC)

*Status of Support: Active (New)

Project Number: W81XWH-22-2-0018

Name of PD/PI: Tagawa, Scott

*Source of Support: Department of Defense

*Primary Place of Performance: Weill Cornell Medicine, NY, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 9/30/22 – 9/29/26

* Total Award Amount (including Indirect Costs):

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.8
2. 2024	1.8
3. 2025	1.8
4. 2026	1.8

Title: Clonal Hematopoiesis as a Determinant for Bone Marrow Toxicities for Targeted Radiation Therapies in Prostate Cancer
Major Goals: Goal is to identify clonal hematopoiesis mutation signatures that predict short term and long-term bone marrow toxicities from targeted radiation therapies (TRT) in prostate cancer

Status of Support: Active (New)

Project Number: W81XWH-22-1-0375

Name of PD/PI: Desai, Pinkal

Source of Support: DoD

Contracting/Grants Officer: Joshua D. McKean

Primary Place of Performance: Weill Cornell Medical College, New York

Project/Proposal Start and End Date: (MM/YYYY) (if available): 9/30/22-9/29/25

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.2 calendar
2. 2024	1.2 calendar
3. 2025	1.2 calendar

Ended

R01CA207645 (Osborne)
A new technique to make 68GA-labeled pharmaceuticals widely available for clinical use.
NIH/NCI
Effort: 0.36 calendar
Grants Officer: George Redmond, redmondg@mail.nih.gov
07/22/2016-06/30/2020
Project Goals/Aims: This proposal aims to establish a new technology for the production and distribution of a prostate cancer imaging agent based on the short-lived radioisotope Gallium-68. The new technology allows for the production of about 100 times larger quantities of Gallium-68 than existing techniques.
Role: Co-Investigator

W81XWH-18-1-0527 (Tagawa/ Beltran/ Bander)*
Molecular and clinical correlates with prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy
Department of Defense
Effort: 1.20 calendar
Grants Officer: Janet P. Kuhns, janet.p.kuhns.civ@mail.mil
09/30/2018-09/29/2021
Project Goals/Aims: The goal of this project is to determine the best genomic, clinical, and imaging characteristics for successful PSMA-TRT and described immune response from PSMA-TRT. Specific Aims: 1. Prospectively and retrospectively assess genomic biomarkers and gene expression changes associated with outcome from anti-PSMA targeted radionuclide therapy. 2. Prospectively and retrospectively assess clinical parameters associated with outcome from anti-PSMA- TRT. 3. Prospectively and retrospectively assess PSMA expression as determined by PSMA molecular imaging associated with response to anti-PSMA -TRT. 4. Evaluate generation of an immune response following anti-PSMA-TRT in association with clinical outcome.
Role: Principal Investigator

2014 Movember -PCF GTSC Award (Armstrong/Nanus)
Development of Circulating Molecular Predictors of Chemotherapy and Novel Hormonal Therapy Benefit in Men with Metastatic Castration Resistant Prostate Cancer (mCRPC)
Supporting Agency: Prostate Cancer Foundation
Effort: 0.60 calendar
Grants Officer: Howard R. Soule, Prostate Cancer Foundation; email: hsoule@pcf.org
08/01/2014 – 7/31/2019 (NCE)
Project Goals/Aims: This project aims 1. Assessment of a CRPC molecular taxonomy based on circulating tumor cell (CTC) molecular profiles in men prior to abiraterone acetate (AA) or

enzalutamide therapy and, 2. To describe treatment-emergent CRPC genotypes during AA, enzalutamide, and taxane-based therapy using longitudinal CTC and circulating biomarkers.
Role: Co-Investigator

W81XWH-09-1-0596 (Tagawa)
Title: A Randomized Phase 2 Trial of 177Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer
Supporting Agency: Department of Defense
Effort: 1.20 calendar
Grants Officer: Janet P. Kuhns; janet.p.kuhns.civ@mail.mil
Performance Period: 8/17/2009-08/16/2020 (NCE)
Level of Funding:
Project Goals/Aims: To demonstrate a difference in the proportion of men with radiographically evident metastatic disease at 18 months in those receiving anti-PSMA-based RIT vs placebo.
Role: Principal Investigator

What other organizations were involved as partners?

Columbia University Medical Center

8. SPECIAL REPORTING REQUIREMENTS

N/A

9. APPENDICES

N/A