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TITLE: Molecular and Clinical Correlates with Prostate-Specific Membrane Antigen (PSMA)-
Targeted Radionuclide Therapy

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CONTRACTING ORGANIZATION: Weill Medical College of Cornell University, New York, NY

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14. ABSTRACT Prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy (TRT) builds upon the radiosensitivity of prostate cancer with the specific expression of PSMA. We hypothesize that there are patient (germline) and/or tumor molecular characteristics such as DNA repair defects and active AR signaling as well as clinical characteristics that are associated with response (or lack thereof) to PSMA-TRT. We hypothesize that quantitative molecular imaging assessment of PSMA expression will be associated with response to PSMA-TRT. We also hypothesize that PSMA-TRT generates an immune response that may be identified and associated with patient outcome. In this proposal, we will utilize our retrospective and prospective data and sample sets to: (i) assess genomic biomarkers and gene expression changes associated with outcome from anti-PSMA targeted radionuclide therapy; (ii) assess clinical parameters associated with outcome from anti-PSMA- TRT; (iii) assess PSMA expression as determined by PSMA molecular imaging associated with response to anti-PSMA -TRT; and (iv) evaluate generation of an immune response following anti-PSMA-TRT in association with clinical outcome. This project addresses the overarching challenge to develop effective new treatments and address mechanisms of resistance and particularly addresses the Focus Areas of Imaging and Targeted Radionuclide Therapy and Therapy and Mechanisms of Resistance and Response. As it is clear that prostate cancer is a radiosensitive disease, and PSMA is highly and selectively expressed, but not all patients respond to PSMA TRT.					
15. SUBJECT TERMS None listed.					
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1. INTRODUCTION:

Prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy (TRT) is a promising new class of drugs for men with metastatic prostate cancer. PSMA is an ideal target because its expression is highly specific for prostate cancer, it is expressed by the vast majority of hormone naïve and castration resistant tumors, and its cell surface expression lends opportunities for both imaging and therapy. Based on promising data led by our team and others looking at PSMA radionuclide therapy, ¹⁷⁷Lu-PSMA-617 has reported preliminary data for a randomized phase 2 study and has completed enrollment on a phase 3 registration trial for men with castration resistant prostate cancer. While the field is excited and encouraged by anti-tumor activity, there is still much to learn about patient and/or tumor molecular characteristics associated with response (or lack thereof) to PSMA-TRT. In this study, we are evaluating genomic biomarkers, clinical features, and PSMA molecular imaging of prospective cohorts of men treated with PSMA radionuclide therapy on our clinical trials.

2. KEYWORDS:

Prostate cancer specific membrane antigen (PSMA), metastatic prostate cancer, radionuclide therapy, biomarkers, genomics
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3. ACCOMPLISHMENTS:

What were the major goals of the project?

Our goal is to define molecular biomarkers and clinical features associated with outcomes from anti-PSMA targeted radionuclide therapy. We are performing prospective and retrospective genomic analyses of archival tissues, plasma samples, and metastatic biopsies from patients treated on prospective anti-PSMA targeted radionuclide clinical trials, with correlation of genomics with outcomes including PSA and radiographic response, progression free survival (PFS), and overall survival. We are also correlating genomics with PSMA PET/CT imaging to evaluate genomic characteristics associated with PSMA low or PSMA-heterogeneous disease and resistance to PSMA radionuclide therapy. PSMA expression and other imaging parameters are being quantified and correlated with response and outcomes. Immune responses following anti-PSMA targeted radionuclide therapy are also being measured, including an assay to measure serologic immunoreactivity to a targeted panel of antigens before/after PSMA-TRT. Overall this project will provide unprecedented insights into the molecular mediators of response and resistance to PSMA targeted radionuclide therapies with broad implications for the field.

What was accomplished under these goals?

We have made the following progress on our Aims according to our SOW:

Aim 1: To prospectively and retrospectively assess genomic biomarkers associated with outcome from anti-PSMA targeted radionuclide therapy

Major Task 1-1: Characterize genomic landscape of prior patients with mCRPC treated with PSMA-TRT [Tagawa and Beltran]

In the initial portion of this Aim, we analyzed clinically available genomic alterations in our retrospective dataset. The subset analyzed with whole exome sequencing (WES) and the larger dataset analyzed across CLIA-approved next generation sequencing platforms were reported in presentations at major scientific conferences in 2019 as described in section 1b (Reportable Outcomes) above.

We have completed subtask 1 for this Aim.

Subtask 2 is underway with results expected in late 2020.

Subtask 3 will occur following completion of subtask 2.

Major Task 1-2: Characterize genomic landscape of prospective patients with mCRPC treated with PSMA-TRT [Tagawa and Beltran]

Subtask 1 is partially complete and will be completed once accrual to the associated therapeutic clinical trials is completed.

Subtask 2 is partially complete and will be completed once accrual to the associated therapeutic clinical trials is completed.

Subtask 3 is planned following completion of subtasks 1 and 2. DNA sequencing of baseline specimens from the initially enrolled patients is occurring in fall, 2020.

Subtask 4 will occur following completion of subtask 3.

Progress to date: Because of the DNA damaging effects of ionizing radiation and of the relationship between the AR pathway and PSMA expression, we hypothesized that patients with germline or somatic gene alterations in DNA damage repair (DDR) pathways or DDR crosstalk pathways (AR, MYC) treated with PSMA-TRT may demonstrate differential treatment responses and outcomes. **Methods:** We examined a cohort of advanced PC patients with available germline (targeted) or/and somatic (targeted or whole exome) DNA testing, and clinical data (Halabi CALGB prognostic factors) and outcome. The Kaplan-Meier method and Cox regression analysis were used to evaluate the associations between mutations/copy number alterations (CNA) with PSA response ($\geq 50\%$, $\geq 30\%$, any) and radiographic response, progression-free survival (PFS) and overall survival (OS). Stepwise forward-selection method was used in the multivariable regression model and p value for entry was set at 0.1. For final analyses, a $p \leq 0.05$ was used for statistical significance. We analyzed 53 patients treated with PSMA-TRT. 16 (30.2%) received ^{177}Lu -J591, 28 (56.6%) ^{177}Lu -PSMA-617, 4 (7.5%) both concurrently, 2 (3.8%) received ^{225}Ac -J591 (3 additional received more than 1 agent sequentially and are analyzed based upon 1st drug). 6 (11.3%) had pathogenic germline DDR mutations while 31 (58.5%) had ≥ 1 mutation/CNA in DDR genes. The most frequently affected DDR genes were: TP53 (n=21, 39.6%), BRCA2 (n=14, 26.4%), CHEK2

(n=10, 18.9%), FANCA (n=10, 18.9%), RB1 (n=9, 16.9%), ATM (n=5, 9.4%), ERCC5 (n=5, 9.4%), ERCC3 (n=3, 5.7%), ERCC2 (n=2, 3.8%), BRCA1(n=2, 3.8%), MSH6 (n=2, 3.8%), FANCD2 (n=2, 3.8%), FANCF (n=2, 3.8%). AR amplifications or resistance-mutations were found in 22 patients (41.5%), and MYC amplifications in 9 patients (16.9%). 19 (35.8%) patients had $\geq 50\%$ PSA decline, 24 (45.3%) experienced $\geq 30\%$ decline and 39 (73.6%) had any PSA decline following PSMA-TRT. 4 patients experienced a partial response while 18 had stable disease. Presence of BRCA2 inactivating mutations, deletions or losses was associated with any PSA decline (p=0.011). PFS was significantly longer in patients with RB1 deletion or loss (5 vs 3 mos, p=0.003). The presence of BRCA2 alterations was predictive of longer OS compared to wild-type patients (49 vs 17 mos, p=0.09). AR amplifications or resistance-mutations and MYC amplifications were both predictive of shorter OS (AR: 13 vs 63 mos, p=0.02; MYC: 8 vs 24 mos, p=0.06). On multivariate analysis, after adjusting for Halabi prognostic groups (low vs high risk), BRCA2 and AR alterations retained their significance as independent prognosticators of OS (BRCA2 HR 0.1 [0.02-0.42], p=0.002; AR HR 7.2 [2.09-25.14], p=0.002). We are now extracting DNA and performing targeted sequencing via the PCF SELECT platform utilizing pre-treatment plasma specimens obtained from the initial subset of patients enrolled in clinical trials. In addition, a larger number of archival tissue specimens from more recently enrolled/treated clinical trial subjects is also being processed. A similar analysis as above will be conducted using the clinical information. **Conclusions:** Knowledge of molecular alterations in BRCA2, AR and RB1 genes may have potential utility for prediction of clinical outcomes in patients being considered for anti-PSMA targeted radionuclide therapies. We are expanding on these finding in larger and prospective cohorts as described above.

Aim 2: To prospectively and retrospectively assess clinical parameters associated with outcome from anti-PSMA targeted radionuclide therapy.

Major Task 2-1: Associate clinical characteristics of patients with mCRPC with outcome from PSMA-TRT [Tagawa and Beltran]

Subtask 1 is complete.

Subtask 2 is partially complete and will be completed once accrual to the associated therapeutic clinical trials is completed.

Subtask 3 is underway in the retrospective cohort and will be completed in the prospective cohort once patient follow up on the associated therapeutic clinical trials is completed.

Progress: We evaluated 46 pts treated with PSMA targeted therapies between 2007-2018 after progression on at least two therapeutic lines, including abiraterone or enzalutamide (76.1%). 28 (60.9%) pts were Halabi high-risk group. PSA decline by at least 50% was observed in 34.8%, median PFS was 5.77 months (95% CI 4.33-7.28), and median OS was 19.15 months (95% CI 12.23-51.25). WES data (n=28) showed an incidence of AR, BRCA1, BRCA2, ATM alterations (copy number variations and point somatic mutations) in 71.4% (n=20), 11.1% (n=3), 29.6% (n=8), and 14.3% (n=4), respectively. Variables found with backward selection with AIC

criterion for PFS and OS suggest significant clinical and molecular predictors of PFS/OS (Table 1). **Conclusion:** Knowledge of previous therapy with AR-directed drugs, baseline LDH, ALP, and AR and BRCA1/BRCA2 alterations may have potential clinical utility in patients being considered for anti-PSMA therapies.

Table 1. Predictors of PFS and OS in advanced prostate cancer patients treated with PSMA targeted therapy

Backward stepwise selection for PFS			Backward stepwise selection for OS		
Variable	HR (95% CI)	P	Variable	HR (95% CI)	P
Previous abi/enza	2.75 (0.93,8.08)	0.067	Previous abi/enza	6.78 (1.17,39.21)	0.032
Baseline LDH	1.01 (1.00,1.02)	0.003	Baseline ALP	1.02 (1.01,1.04)	<0.001
BRCA1 alteration	0.05 (0.01,0.53)	0.012	BRCA2 alteration	0.07 (0.01,0.53)	0.010
BRCA2 alteration	0.26 (0.09,0.76)	0.014	AR alteration	8.38 (1.26,55.84)	0.028

Aim 3: To prospectively and retrospectively assess PSMA expression as determined by PSMA molecular imaging associated with response to anti-PSMA targeted radionuclide therapy

Major Task 3-1: Associate clinical characteristics of prior patients with mCRPC with outcome from PSMA-TRT [Tagawa and Bander]

Subtask 1 is complete and has been reported in a presentation at a major scientific conference in 2019 as described in Section 6 below. A full manuscript has been written and submitted for peer review. Data are summarized below.

Subtask 2 is underway and will be completed once accrual and follow up on the associated therapeutic clinical trials is completed.

Progress: We analyzed images and clinical outcome from 215 men receiving PSMA-TRT. Higher PSMA expression as determined by PSMA imaging was associated with a higher likelihood of response to treatment (p=0.006) on univariate analysis. On multivariable analysis, stronger PSMA imaging remained associated with response even after controlling for clinical prognostic factors, radioactive dose administered, and prior chemotherapy (p=0.006). However, a small subset with no or limited PSMA expression as determined by imaging had PSA response. **Conclusion:** These data support the hypothesis that high PSMA uptake on imaging is associated with response to PSMA-TRT.

Aim 4: To evaluate generation of an immune response following anti-PSMA targeted radionuclide therapy in association with clinical outcome

Major Task 4-1: To assay serologic immunoreactivity to a targeted panel of antigens before/after PSMA-TRT and associate with outcome [Tagawa and Bander]

Collection of specimens for subtasks 1 and 2 is underway.

Analysis will be completed once accrual to the associated therapeutic clinical trials is completed. The initial batch of specimens is expected to undergo analysis by early 2021.

Major Task 4-2: To assay serologic immunoreactivity against a broad array of antigens before/after PSMA-TRT and associate with outcome. [Tagawa and Bander]

Subtask 1 was attempted, but unsuccessful due to loss/damage of old serum.

Collection of specimens for subtask 2 is underway

Analysis will be completed once accrual to the associated therapeutic clinical trials is completed.

Major Task 4-3: To assess immunogenic cell death following PSMA-TRT

Subtask 1 was attempted, but unsuccessful due to loss/damage of old serum. [Tagawa and Bander]

Collection of specimens for subtasks 2 and 3 is underway

Analysis will be completed once accrual to the associated therapeutic clinical trials is completed. The initial batch of specimens is expected to undergo analysis in early 2021.

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

Trainees and fellows in our groups participate and lead analyses related to this study. Through meetings and interactions between scientific and clinical investigators, trainees and fellows are provided unique learning opportunities in translational research. Dr. Conteduca and Dr. Vlachostergios were first authors and presented abstracts on findings from this study at GU ASCO, AACR, and ASCO in 2019 and were co-authors of abstracts presented in 2020. Dr. Vlachostergios is first-author of the manuscript on PSMA imaging and response to PSMA-TRT which is undergoing peer review.

How were the results disseminated to communities of interest?

Results were presented as meeting abstracts at four national/international meetings in 2019 and 2020 (GU ASCO, AACR, ASCO, and ESMO). We have also participated in meetings, seminars, and interviews to disseminate results including through the Prostate Cancer Foundation and UroToday.

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

The study tasks above are in progress and on track. We anticipate continued progress this year on optimizing assay performance and in our analysis of data. We plan to present new findings at national /international meetings and to publish results.

4. IMPACT:

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

PSMA targeted radionuclide therapy is a promising drug approach for men with metastatic castration resistant prostate cancer. This study is providing new insights into molecular mediators of response and resistance to PSMA targeted radionuclide therapy, which may help in the future to select the patients most likely to benefit and to inform the development of effective combination strategies to prevent or target resistance mechanisms. The planned genomic analyses and correlation with imaging and immune markers will also provide new knowledge on tumor heterogeneity and how host responses impact therapy response and progression.

What was the impact on other disciplines?

Results from this project may provide insights into biomarker of response / resistance to radionuclide targeted therapies in other tumor types.

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

Due to multiple communication issues, HRPO approval was delayed (initial communication was that a separate protocol was not necessary). This has now been resolved.

Two subaims involved previously collected and frozen serum from subjects enrolled in prior clinical trials.

This serum was unfortunately lost and those subaims will not be able to be performed.

We had planned to extract DNA and perform targeted sequencing of samples in spring, 2020. However that was delayed due to the COVID-19 pandemic. We plan to perform these studies in late 2020.

We had planned to analyze serum samples for immunologic assays in spring, 2020. However that was delayed due to the COVID-19 pandemic. We plan to perform these studies by early 2021.

Changes that had a significant impact on expenditures

Nothing to report

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

Nothing to report

Significant changes in use or care of human subjects

The clinical trials associated with these studies have been affected by the COVID-19 pandemic. We anticipated completion of enrollment in the first half of 2020, but enrollment to the clinical trials was delayed by the pandemic. We anticipate completing enrollment by early 2021.

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Miyahira AK, Pienta KJ, Babich JW, Bander NH, Calais J, Choyke P, Hofman MS, Larson SM, Lin FI, Morris MJ, Pomper MG, Sandhu S, Scher HI, Tagawa ST, Williams S, Soule HR. Meeting Report from the Prostate Cancer Foundation PSMA Theranostics State of the Science Meeting. *The Prostate* 2020

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

Other publications, conference papers and presentations.

Vincenza Conteduca, Clara Oromendia, Panagiotis J. Vlachostergios, Amy Hackett, Charlene Thomas, Aidan Case, Jyothi Manohar, Kenneth Eng, Andrea Sboner, Karla V. Ballman, Olivier Elemento, David M. Nanus, Himisha Beltran, Scott T. Tagawa. Clinical and molecular analysis of patients treated with prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy. Presented at the 2019 Genitourinary Cancers Symposium, *J Clin Oncol* 2019

Panagiotis J. Vlachostergios, Vincenza Conteduca, Amy Hackett, Jyothi Manohar, Aileen Lee, Aidan Case, Michael Sun, Muhammad J. Niaz, Olivier Elemento, Ana M. Molina, David M. Nanus, Himisha Beltran, Neil H. Bander, Scott T. Tagawa. Prognostic value of BRCA2 and AR gene alterations in advanced prostate cancer patients treated with PSMA-targeted radionuclide therapies. Presented at the 2019 AACR Annual Meeting.

Panagiotis J. Vlachostergios, Muhammad Junaid Niaz, Seyed Ali Mosallaie, Paul J. Christos, Amy Hackett, Joseph R. Osborne, Yuliya Jhanwar, Lauren Gracey, Ana M. Molina, David M. Nanus, Neil Harrison Bander, Scott T. Tagawa. Association of noninvasive, radiographic measurement of prostate-specific membrane antigen (PSMA) expression with response to PSMA-targeted radionuclide therapy (TRT). Presented during poster discussion session of the 2019 ASCO Annual Meeting, *J Clin Oncol* 2019

S.T. Tagawa, J. Osborne, A. Hackett, M.J. Niaz, V. Cooley, P. Christos, P. Vlachostergios, C. Thomas, L. Gracey, H. Beltran, A. Molina, D.M. Nanus, J. Babich, S. Vallabhajosula, A. O. Sartor, K. Ballman, N.H. Bander. Preliminary results of a phase I/II study of fractionated dose 177Lu-PSMA-617 for progressive

metastatic castration resistant prostate cancer (mCRPC). Presented in poster discussion session of 2019 ESMO annual meeting. *Annals of Oncology* 2019

S.T. Tagawa, J. Osborne, M.J. Niaz, S. Vallabhajosula, P. Vlachostergios, C. Thomas, A. Molina, C.N. Sternberg, S. Singh, E. Fernandez, J. Babich, D.M. Nanus, K. Ballman, N.H. Bander. Dose-escalation results of a phase I trial of ²²⁵Ac-J591 for progressive metastatic castration-resistant prostate cancer (mCRPC). Presented at the 2020 Genitourinary Cancers Symposium, published in supplement to *J Clin Oncol*.

S.T. Tagawa, J. Osborne, C. Thomas, E. Fernandez, M.J. Niaz, S. Vallabhajosula, P. Vlachostergios, A. Molina, C.N. Sternberg, S. Singh, A. Patel, A. Tan, J. Babich, D.M. Nanus, K. Ballman, N.H. Bander. Phase I dose-escalation trial of prostate-specific membrane antigen (PSMA)-targeted alpha emitter ²²⁵Ac-J591 for progressive metastatic castration-resistant prostate cancer (mCRPC). Presented at the 2020 AACR Annual Meeting, published in Proceedings of the 2020 Annual Scientific Meeting of the American Association of Cancer Research.

Niaz MJ, Skafida M, Osborne J, Nanus DM, Molina AM, Thomas C, Vallabhajosula S, Christos P, Bander NH, Tagawa ST. (PD16-11) Comparison of prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy (TRT) with lutetium-177 (¹⁷⁷Lu) via antibody J591 vs small molecule ligand PSMA-617. Presented at the 2020 AUA annual meeting, published in supplement to *J Urol*.

S.T. Tagawa, J. Osborne, E. Fernandez, C. Thomas, M.J. Niaz, S. Vallabhajosula, P. Vlachostergios, A. Molina, C.N. Sternberg, S. Singh, J. Babich, D.M. Nanus, K. Ballman, N.H. Bander. Phase I dose-escalation study of PSMA-targeted alpha emitter ²²⁵Ac-J591 in men with metastatic castration-resistant prostate cancer (mCRPC). Presented at the 2020 ASCO Annual Meeting, published in supplement to *J Clin Oncol*.

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?

Provide the following information for: (1) PDs/Pis; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	Scott Tagawa
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Oversees the entire study
Funding Support:	Weill Cornell Medicine

Name:	Neil Bander
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Oversees entire study, esp immunologic and imaging components

Funding Support: Weill Cornell Medicine
Name: Himisha Beltran
Project Role: PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Oversees genomic portions of the project
Funding Support: Dana Farber Cancer Institute

Name: Escarleth Fernandez
Project Role: Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
Contribution to Project: Coordination of data
Funding Support: Weill Cornell Medicine

Name: Charlene Thomas
Project Role: Coordinator, staff statistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
Contribution to Project: Coordination of data, statistics
Funding Support: Weill Cornell Medicine

Name: Ada Gjyrezi
Project Role: Research technician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Processing biospecimens
Funding Support: Weill Cornell Medicine

Name: Muhammad Niaz
Project Role: Nuclear medicine fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
Contribution to Project: Processing images; coordinating specimens
Funding Support: Weill Cornell Medicine

Name: Michael Sigouros
Project Role: Lab Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
Contribution to Project: Sample Coordination
Funding Support: Weill Cornell Medicine

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

Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Dr. Tagawa has additional support (including PI and co-investigator on additional DOD grants), but without overlap or change in effort on this project.

Dr. Bander has additional involvement as co-investigator on another DOD grant, but with no overlap or change in effort on this project.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

This documentation has been added above for our joint submission.

QUAD CHARTS:

9. APPENDICES: