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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, this proposal will rapidly translate into clinical progress for men afflicted with advanced prostate cancer in the near term. Furthermore, such targeted therapy may lead to future cures for men with micrometastatic disease in the high-risk clinically localized or biochemically recurrent settings.

15. SUBJECT TERMS

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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, ^{177}Lu--PSMA-617 is now completing a phase 3 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.

Please note that this year minimal funds were spent on the project as we applied for a no-cost extension. In the application for the extension, we described delays in coordinating blood /tissues and DNA/RNA sequencing for the proposed correlative analyses and delays in hiring that were largely related to the COVID pandemic. We are poised to continue working on the proposed aims during the no cost extension period. In the past year, we have added to the discoveries made with support from this grant. These new discoveries are outlined in this report. Otherwise, we have largely kept intact the narrative of our work to date.

2. KEYWORDS:

Prostate cancer specific membrane antigen (PSMA), metastatic prostate cancer, radionuclide therapy, biomarkers, genomics

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 as described in Products.

We have completed subtask 1 for this Aim.

Subtask 2 has been completed, with extraction of DNA occurring in 2021.

Subtask 3 occurred in 2022, with analysis ongoing and public reporting of data later in the year.

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 follow up on the associated therapeutic clinical trials is completed.

Subtask 2 is partially complete and will be completed; all baseline specimens have been collected and processed. Follow up specimens will be processed once follow up on the associated therapeutic clinical trials is completed.

Subtask 3 has been completed on baseline specimens; processing of post-treatment specimens will be completed once follow up on the associated therapeutic clinical trials is completed (after subtasks 1 and 2 completed for follow up specimens).

Subtask 4 Analysis of baseline data is ongoing with preliminary results presented at ESMO 2022

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 (≥50%, ≥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 ≥50% PSA decline, 24 (45.3%) experienced ≥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 have recently extracted DNA and performed 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 has been processed, with targeted genomic sequencing performed via the Oncomine platform. 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.

Associations Between Circulating Tumor DNA (ctDNA) and Prognosis After Prostate-Specific Membrane Antigen (PSMA) Targeted Radionuclide Therapy (TRT)

Background: Following approval of 177Lu-PSMA-617 for mCRPC, PSMA TRT is becoming standard of care in advanced prostate cancer. Even after pre-selection by PSMA imaging, not all patients respond, and some patients who progress on PSMA TRT nevertheless retain high expression as assessed by imaging. Prognostic genomic factors may exist and account for differential responses to PSMA TRT. Collection of real-time tissue biopsies in mCRPC presents challenges that could be overcome with ctDNA assays.

Methods: Plasma DNA and matched control DNA were obtained prior to treatment in two prospective PSMA TRT trials [Tagawa et al. ESMO 2021; Tagawa et al. ASCO 2021] and assayed utilizing the PCF_SELECT platform [Orlando et al., NAR Cancer 2022]. Variables of interest included *AR* copy number (CN; wild-type vs gain), homologous recombination repair (HRR) gene CN (wild-type vs loss), and allele-specific ploidy (asP; diploid vs high; asP ≤ 2.5 and asP > 2.5, respectively). asP is a novel metric for genomic instability, computed as the weighted mean of the allele-specific CN of homologous chromosomes [Ciani et al., Cell Syst 2022]. Cox regression modelling was used to assess association of these variables with clinical outcome measures of >50% PSA response (PSA50), biochemical progression-free survival (bPFS), and OS.

Patient Characteristics	N = 80
Median PSA (ng/mL)	169.62 (range 4.42 – 7168.41)
Median Age at Treatment	70 (range 52 – 91)
Halabi Risk Category	
Low	2 (2.5%)
Intermediate	20 (25%)
High	58 (72.5%)
Therapy	
^{225}*Ac-J591*	30 (37.5%)
^{177}*Lu-PSMA-617*	50 (62.5%)
Prior Taxane Chemotherapy	47 (58.75%)
Median Prior ARPI	2
Lymph Node Metastasis	65 (81.25%)
Liver Metastasis	17 (21.25%)
Lung Metastasis	17 (21.25%)
Bone Metastasis	76 (95%)
High asP	40 (50%)
***AR* Status**	
Wild-Type	29 (36.25%)
Non-Synonymous SNV	28 (35%)
Copy-Number Gain	33 (41.25%)
***TP53* Non-Synonymous SNV**	22 (27.5%)
***BRCA2* Non-Synonymous SNV**	8 (10%)
***BRCA2* Loss**	11 (13.75%)
HRR Gene Aberration	47 (58.75%)

Table 1. Characteristics of patients included in this analysis. ARPI = androgen receptor pathway inhibitor. SNV = single nucleotide variant. HRR gene aberration defined as either copy-number loss or non-synonymous SNV in at least one gene involved in homologous recombination repair (HRR; *ATM, BRCA1, BRCA2, RAD51B, RAD51C, TOP3B*).

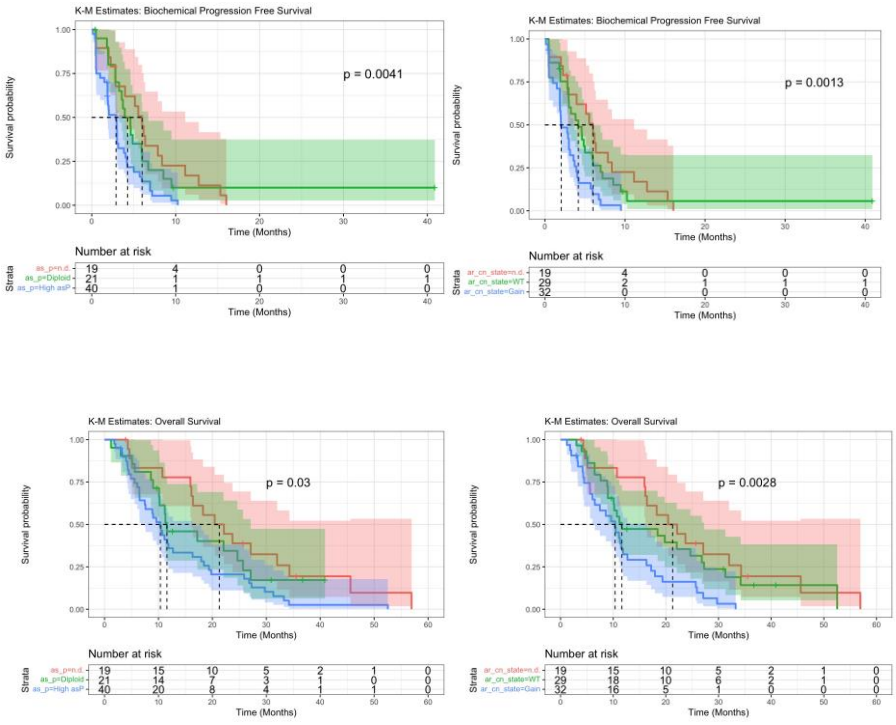

Figure 2. Kaplan-Meier survival curves depicting associations between high asP (right)/AR gain (left) and OS.

Variables	HR (95% CI)	*P* value
asP *High vs WT/ND*	2.42 (1.34-4.38)	0.003
AR *Gain vs WT/ND*	2.78 (1.5-5.17)	0.001
TP53 *SNV vs WT/ND*	1.34 (0.79-2.27)	0.27
Tumor Content *0.5-1 vs lower*	3.23 (1.62-6.41)	<0.001

Variables	HR (95% CI)	*P* value
asP *High vs WT/ND*	2.15 (1.17-3.92)	0.013
AR *Gain vs WT/ND*	2.74 (1.44-5.21)	0.002
TP53 *SNV vs WT/ND*	1.42 (0.85-2.38)	0.18
Tumor Content *0.5-1 vs lower*	2.93 (1.47-5.83)	0.002

Table 2. Univariate analysis in relation to bPFS (left) and OS (right).

Results: On univariate analysis, high asP and *AR* gain negatively correlated with bPFS and OS (Figures 1

and 2; Table 2). ctDNA quantity was associated with worse bPFS and OS (Table 2). There was a trend toward *TP53* SNV and poorer bPFS and OS (Table 2). There was a trend toward high asP and lower rates of PSA50 (OR 0.48; 95% CI 0.16-1.47; p=0.20). There was also a trend toward *AR* gain and lower rates of PSA50 (OR 0.47; 95% CI 0.14-1.49; p=0.20). Controlling for circulating tumor DNA fraction on multivariable analysis, there was a trend toward high asP and worse bPFS (HR 1.78; 95% CI 0.87-3.66; p=0.12) and OS (HR 1.38; 95% CI 0.64-2.96; p=0.4). On multivariable analysis, there was a trend toward *AR* gain and worse bPFS (HR 2.08; 95% CI 0.99-4.35; p=0.053) and OS (HR 1.73; 95% CI 0.8-3.75; p=0.2).

Conclusions: ctDNA analysis – a non-invasive technique – in patients undergoing PSMA TRT demonstrates that *AR* CN gain and high asP, reflecting genomic instability and potentially complex karyotype, are associated with poorer prognosis. ctDNA quantity may also be prognostic in patients receiving PSMA TRT.

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).

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

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.

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 and published in a peer reviewed journal as described Products below.

Subtask 2 is underway and has been partially completed as described below.

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. These data were initially presented in 2019 and published in 2021.

Preliminary analysis of pre-treatment PSMA imaging has been performed on the individual trials as presented at ASCO 2021 (for 225Ac-J591 and ESMO 2021 (for 177Lu-PSMA-617). A combined analysis was presented at the Society of Urologic Oncology annual meeting.

Conclusion: These data support the hypothesis that high PSMA uptake on imaging is associated with response to PSMA-TRT, but there are a small subset with poor pre-treatment imaging that may respond 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 has undergone analysis.

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 being analyzed.

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 manuscripts on PSMA imaging and response to PSMA-TRT as well as PSMA imaging and prognosis in mCRPC which were published in 2021.

How were the results disseminated to communities of interest?

Results were presented as meeting abstracts at four national/international meetings in 2019, 2020, 2021, 2022 (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 with somewhat of a delay in completion of both clinical trial enrollment as well as assay performance due to the COVID-19 pandemic. We anticipate continued progress this year on completing 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 recently approved 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 completed initial batches of these studies in late 2021/2022.
We had planned to analyze serum samples for immunologic assay. However that was delayed due to the COVID-19 pandemic.

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

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 completed enrollment in early 2021 and subjects are in follow up.

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:

Journal publications.

Miyahira AK, Pienta KJ, Morris MJ, Bander NH, Baum RP, Fendler WP, Goeckeler W, Gorin MA, Hennekes H, Pomper MG, Sartor O, Tagawa ST, Williams S, Soule HR. Meeting report from the Prostate Cancer Foundation PSMA-directed radionuclide scientific working group. Prostate. 2018 Aug;78(11):775-789. doi: 10.1002/pros.23642. Epub 2018 May 1. PMID: 29717499.

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 Aug 31. Doi: 10.1002/pros.24056. Online ahead of print. PMID: 32865839

Vlachostergios PJ, Niaz MJ, Skafida M, Mosallaie SA, Thomas C, Christos PJ, Osborne JR, Molina AM, Nanus DM, Bander NH, Tagawa ST. Imaging expression of prostate-specific membrane antigen and response to PSMA-targeted beta-emitting radionuclide therapies in metastatic castration-resistant prostate cancer. *The Prostate* 2021 Apr; 81(5): 279-285. doi: 10.1002/pros.24104. Epub 2021 Jan 19. PMID 33465252.

Vlachostergios PJ, Niaz MJ, Sun MJ, Mosallaie SA, Thomas C, Christos PJ, Osborne JR, Molina AM, Nanus DM, Bander NH, Tagawa ST. Prostate-specific membrane antigen (PSMA) uptake and survival in metastatic castration-resistant prostate cancer. *Frontiers in Oncology* 2021 Feb 18. doi: 10.3389/fonc.2021.630589.

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 ^{225}Ac-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 emiter ^{225}Ac-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 (^{177}Lu) 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 emiter ^{225}Ac-J591 in men with metastatic castration-resistant prostate cancer (mCRPC). Presented at the 2020 ASCO Annual Meeting, published in supplement to *J Clin Oncol*.

S.T. Tagawa, M. Sun, A.O. Sartor, C. Thomas, S. Singh, M. Bissasar, E. Fernandez, M.J. Niaz, B. Ho, S. Vallabhajosula, J. Babich, A. Molina, C.N. Sternberg, D.M. Nanus, J. Osborne, N.H. Bander. Phase I study of ^{225}Ac-J591 for men with metastatic castration-resistant prostate cancer (mCRPC). Presented at a poster discussion session of the 2021 ASCO Annual Meeting, published in supplement to *J Clin Oncol*.

S.T. Tagawa, M. Sun, A.O. Sartor, C. Thomas, A. Molina, C.N. Sternberg, D.M. Nanus, J. Osborne, N.H. Bander. Final results of a phase I/II trial of fractionated dose 177Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer (mCRPC). Presented at the 2021 ESMO annual meeting, published in supplement to *Annals of Oncology* 2021

Michael Sun[1]; Charlene Thomas[2]; Francesco Orlando[6]; Sharon Singh[1]; Mahelia Bissassar[1]; Michael Sigouros[3]; Gerhardt Attard[5]; Joseph Osborne[4]; Jones Nauseef[1,3]; Ana M. Molina[1]; Cora N. Sternberg[1,3,4]; David M. Nanus[1,4]; Francesca Demichelis[6]; Himisha Beltran[7]; Neil H. Bander[1,4]; Scott T. Tagawa[1,4] [1]Division of Hematology and Medical Oncology, [2]Department of Biostatistics, [3]Englander Institute for Precision Medicine, [4]Department of Urology, Weill Cornell Medicine, New York, NY, USA; [5]UCL Cancer Institute, University College London, London, England; [6]Department of Cellular, Computational and Integrative Biology, University of Trento, Trento, Italy; [7]Dana-Farber Cancer Institute, Boston, MA, USA , Associations Between Circulating Tumor DNA (ctDNA) and Prognosis After Prostate-Specific Membrane Antigen (PSMA) Targeted Radionuclide Therapy (TRT), Presented at the 2022 ESMO annual meeting, published in supplement to Annals of Oncology 2021

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?

Name:	Himisha Beltran
Project Role:	PI

Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Genomic studies including DNA/RNA profiling of tumor samples and ctDNA, sequencing and analysis.
Funding Support:

Name: Maria Mica Garcia
Project Role: Research Technician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4
Contribution to Project: DNA/RNA extraction, QC analysis, library preparation and preparing the samples sequencing.
Funding Support:

Name: Varadha Balaji Venkadakrishnan
Project Role: Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Work with other members of the team to analyze and prioritize data for validation.
Funding Support:

Name: Yasutaka Yamada
Project Role: Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Work with other members of the team to analyze and prioritize data for validation.
Funding Support: Japan Society for the Promotion of Science Overseas Research Fellowship

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

Beltran, Himisha
PREVIOUS (past five years):

ENDED
DFCI SRA-21-0376 05/2021 – 12/2022 0.12 CM
Bristol Myers Squibb $99,365
Restoration of Antigen Presentation, Innate Immune Signaling, and Cellular Differentiation by Epigenetic Inhibitors in Small Cell Lung and Neuroendocrine Prostate Cancer
Specific Aims: 1) Identify the relative impact of LSD1 inhibitors or EZH2 inhibitors treatment on derepression of MHC class I, markers of innate immune signaling, and loss of neuroendocrine differentiation across multiple preclinical models of small cell lung cancer (SCLC) and neuroendocrine prostate cancer; 2) Determine whether LSD1 and EZH2 inhibition synergize to derepress MHC class I, innate immune signaling, and cause loss of neuroendocrine differentiation.
Role: Principal Investigator
POC: Protocol Manager: Donette Quamina-Edghill; donette.quaminaedghill@bms.com; 609-302-4189

CURRENT:

AWARDED
22CHAL08 01/06/23 – 01/05/25 0.60 CM
Prostate Cancer Foundation $1,000,000
Mechanisms of Response and Resistance to DLL3-Targeted T Cell Engager Therapy
Specific Aims: 1) Improve patient selection for a DLL3-targeted T cell engager therapy; 2) Investigate the therapeutic potential of DLL3-Targeted T cell engagers and resistance mechanisms.
Role: Principal Investigator
POC: Program Administration Manager: Audrey Gardener; agardner@pcf.org; 310.570.4792

AWARDED
22TACT02 (Lewis) 01/01/23 – 12/31/25 0.60 CM
Prostate Cancer Foundation $900,000
Novel theranostic agents for neuroendocrine prostate cancer
Specific Aims: 1) Dr. Beltran and her team will be responsible for leading correlative studies in Aim 1 including tissue profiling of DLL3 positive and DLL3 negative metastatic tumor lesions identified by PET and blood-based correlatives; 2) Dr. Beltran will use organoid models to validate hits identified in Aim 4; 3) Dr. Beltran will contribute to all aspects of data analysis and interpretation.
Role: Co-Investigator
POC: Program Administration Manager: Audrey Gardener; agardner@pcf.org; 310.570.4792

AWARDED
22003-01 01/01/23 -06/30/24 0.12 CM
DDTRP $580,000
Project 2, Dissecting Tumor Heterogeneity in Lethal Castration Resistant and Neuroendocrine Prostate Cancer
Specific Aims: 1) Understand the interplay between epigenetics and metabolism of liver versus non-liver metastases in adenocarcinoma and non-adenocarcinoma CRPC; 2) Map tumor transcriptomic and metabolomic profiles as prostate cancer evolves from a mixed adeno-NE tumor to NEPC.
Role: Co-Principal Investigator

POC: DDTRP Program Administrator: Sylvia Lin; 617-632-5599; Sylvia_Lin@dfci.harvard.edu

AWARDED
NFCR 12/01/22-11/30/23 0.12 CM
NFCR $110,000
To develop a non-invasive approach to detect clinically relevant phenotypic subtypes of prostate and kidney cancers
Specific Aims: 1) To perform molecular subtyping of kidney cancer using CTCs; 2) To detect the NEPC features using CTCs.
Role: Co-Principal Investigator
POC: Direct of Science Relations: Hali Hartmann; 443-474-6294; hhartmann@nfcr.org

AWARDED
P50CA092629 (Scher) 09/01/22 -08/31/27 0.24 CM
National Cancer Institute $133,345
SPORE in Prostate Cancer, Project 3: Therapeutic Targeting of Lineage Plasticity in Castration-Resistant Prostate Cancer
Specific Aims: Dr. Beltran will help oversee ctDNA and tissue methylation aspects of this project and work closely with members of the team to integrate efforts, analyze results, and prioritize data. Her lab will also perform drug testing using patient derived organoids.
Role: Co-Investigator
POC: Program Coordinator, Translational Research Program: Mehvish Khan; khanml l@mail.nih.gov

AWARDED
R01CA270539 (Dehm) 09/01/22 – 08/31/27 0.60 CM
National Institutes of Health $305,845
Targeting early events in prostate cancer lineage plasticity
Specific Aims: 1) There will be 10-20 drugs nominated by Dr. Dehm's lab in Years 1-3 for testing by Dr. Beltran and her team in Years 3-5; 2) Readouts in the PDO assays will be growth/viability, and for certain efficacious drugs some follow-up IF/IHC and RT-PCR for lineage plasticity markers where warranted.
Role: Co-Investigator
POC: Jacquelyn Saval; savalj@mail.nih.gov; 240-276-6312

AWARDED
DFCI SRA-DS-7300 06/01/22 – 05/31/24 0.30 CM
Daiichi Sankyo, Inc. $177,724
Targeting B7-H3 in neuroendocrine prostate cancer
Specific Aims: 1) Determine the anti-tumor activity of DS-7300a, decitabine, and the combination in CRPC/NEPC in in-vitro and in-vivo models; 2) Elucidate the expression and clinical associations of B7-H3 in our patient cohorts and preclinical models of CRPC/NEPC
Role: Principal Investigator
POC: Associate Director, US Medical Affairs, Research and Strategy – Oncology: Diederik van Bodegom; dvanbodegom@dsi.com

AWARDED
DFCI SRA-22-1663 03/24/22 – 03/24/23 0.60 CM
Circle Pharma, Inc. $89,000
Targeting Cyclin-CDK2 complex in RB dysregulated advanced prostate cancer Specific Aims: To define the therapeutic activity of targeting Cyclin-CDK complex Role: Principal Investigator
POC: Vice President, Translational Medicine: Evelyn Wang; evelyn.wang@circlepharma.com; 415-629-9391

What other organizations were involved as partners? Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report

9. APPENDICES:

Nothing to report