

AWARD NUMBER: W81XWH-20-1-0257

TITLE: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)

PRINCIPAL INVESTIGATOR: Dr. Ana Aparicio, MD

CONTRACTING ORGANIZATION: The University of Texas MD Anderson Cancer Center

REPORT DATE: OCTOBER 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE OCTOBER 2023		2. REPORT TYPE Annual		3. DATES COVERED 1SEPT2022 - 31AUG2023	
4. TITLE AND SUBTITLE Chemoinmunotherapy for Aggressive Variant Prostate Cancers (AVPC)				5a. CONTRACT NUMBER W81XWH-20-1-0257	
				5b. GRANT NUMBER PC190353	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. Ana Aparicio, MD E-Mail: aaparicio@mdanderson.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas MD Anderson Cancer Center 1515 Holcombe Boulevard Houston, TX 77030-4009				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
14. ABSTRACT Men with androgen indifferent prostate cancers have a dismal prognosis and limited treatment options. To provide a framework for their study and therapy development, we defined the aggressive variant prostate cancers (AVPC) and in previous studies obtained evidence that men with AVPC benefit from the addition of carboplatin to cabazitaxel chemotherapy, and likely from PARP inhibitor maintenance following chemotherapy induction. Building on this work and based on the evidence of immune-modulation by chemotherapy and PARP inhibitors in preclinical studies, as well as the clinical benefit observed with the addition of immune-checkpoint therapy to chemotherapy in patients with aggressive malignancies that share similarities with the AVPC, we hypothesized that PD-1 inhibition will enhance the anti-tumor response of platinum-based chemotherapy induction and PARP inhibitor maintenance in men with AVPC. To test this hypothesis, we proposed this phase II randomized trial in which men with AVPC are treated with up to 6 cycles of cabazitaxel-carboplatin induction, with the anti-PD1 inhibitor cetrelimab added on Cycle #2 of treatment, and then randomized to the PARP inhibitor niraparib vs niraparib plus cetrelimab maintenance. Tumor biopsies are mandated at 3 timepoints. Our primary objectives are to estimate the progression free survival of men with AVPC in each arm and evaluate the changes in the density and localization of immune markers and cell subsets in tumor biopsies. The study was activated on 12/29/2020. <i>As of 08/27/2023, 93 patients have been treated on trial and 166 biopsy samples have been assembled.</i>					
15. SUBJECT TERMS Prostate cancer, aggressive variant prostate cancers, small cell or neuroendocrine prostate carcinomas, immunotherapy, chemotherapy, carboplatin, cabazitaxel, olaparib, durvalumab, PD-L1					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	42	19b. TELEPHONE NUMBER (include area code);
13. SUPPLEMENTARY NOTES					

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	9
5. Changes/Problems	10
6. Products	11
7. Participants & Other Collaborating Organizations	12
8. Special Reporting Requirements	42
9. Appendices	N/A

ANNUAL REPORT

September 1, 2022 – August 31, 2023

1. INTRODUCTION

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The purpose of this study is to determine the effect of anti-PD1 inhibition (cetrelimab) on the efficacy and immune-modulatory effects of cabazitaxel-carboplatin induction chemotherapy and PARP inhibitor (niraparib) maintenance therapy in men with *aggressive variant prostate cancers* (AVPC).

Up to 120 men with AVPC will be treated with up to 6 cycles of cabazitaxel-carboplatin chemotherapy, to which cetrelimab will be added on cycle 2, in order to randomize 88 to maintenance therapy with niraparib with or without cetrelimab. Tumor biopsies are obtained after cycle 1 (before the addition of cetrelimab), after cycle 3 (once 2 cycles with the combination of chemotherapy and cetrelimab have been completed) and then, after 3 cycles of niraparib with or without cetrelimab are complete.

Efficacy will be determined based on progression free survival, and multiplex immunofluorescence will be used to identify PD-L1, CD4, CD8, CD68 and CD163 expression in tumor biopsies.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Prostate cancer, aggressive variant prostate cancers, small cell or neuroendocrine prostate carcinomas, immunotherapy, chemotherapy, carboplatin, cabazitaxel, niraparib, cetrelimab, PD1

3. ACCOMPLISHMENTS

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Tasks:

1. PREPARE FOR CLINICAL TRIAL ACTIVATION

Milestone: *Clinical trial ready for activation*

- Expected, 09/2020
- Completed, 12/2020 (Funding activated at The University of Texas MD Anderson Cancer Center 01/15/2021)

2. PARTICIPANT RECRUITMENT, TREATMENT AND EVALUATION

Milestone 1. *1st participant consented, screened and enrolled*

- Expected, 10/2020
- Completed, 01/2021

Milestone 2. *Complete accrual (88-120 patients)*

- Expected, 04/2022 for an n=88; revised 05/2024 for an n=120
Note: Accrual was delayed by COVID19 and, given the rate of progression prior to randomization, we will need to accrue up to the full 120 to meet our endpoints. Our rate of accrual in the last 12-month period (since 09/2022) has ranged from 0 to 6 with an average of 3 patients per month. At the current rate, we expect to complete accrual in 05/2024.
- Ongoing, n=93 patients registered to date, 77.5% of planned accrual

Milestone 3. Complete toxicity and efficacy evaluations

- Expected, 10/2023, revised 10/2024

Note: If the last patient is registered in 05/2024, assuming they are randomized to maintenance treatment, by 09/2024 they will undergo biopsy #3 (see below) and will have been on maintenance treatment for 3 months.

- Ongoing

3. SAMPLE COLLECTION AND DISTRIBUTION

Milestone 1. Complete sample collection (88-120 patients)

- Expected, 10/2023, revised 10/2024
- Ongoing

Biopsy #1 (post-cycle #1 cabazitaxel-carboplatin) obtained from **n=76** patients to date.

Biopsy #2 (post-cycle #3 cabazitaxel-carboplatin-cetrelimab) obtained from **n=57** patients to date (note, 4 procedures were aborted because the lesion was too small to biopsy).

Biopsy #3 (post-cycle #9 niraparib with or without cetrelimab) obtained from **n=20** patients to date (note, 1 procedure was aborted because the lesion was too small to biopsy).

Biopsy #4 (optional, end-of-treatment) obtained from **n=6** patients to date.

Biopsy #0 (optional, pre-cabazitaxel-carboplatin) obtained from **n=7** patients to date.

4. MULTIPLEX IF ANALYSIS AND INTERPRETATION

Milestone 1. Complete multiplex IF (mIF) analysis and interpretation

- Expected, 03/2024, revised 03/2025
- We completed NanoString analyses of frozen metastatic biopsy cores obtained at baseline and after 6 cycles of carboplatin-cabazitaxel from men participating in the MDA 2017-0133 CCOLA trial. As shown in Fig. 1. no significant differences in immune cell populations were observed across the groups. It should be noted that these biopsies were not microdissected and that the results have not been corrected for tumor purity.

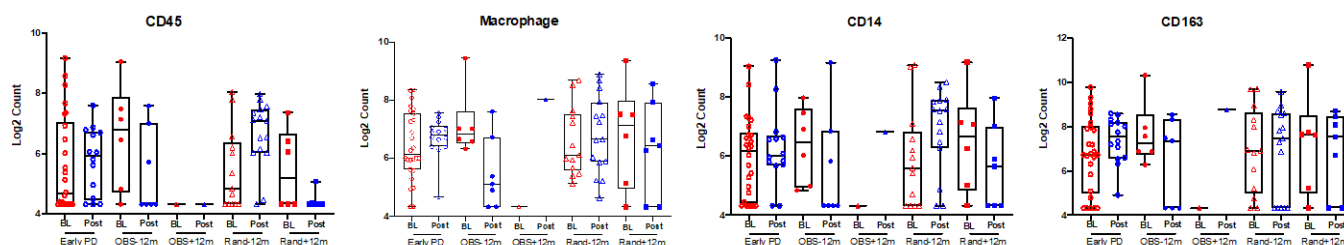


Figure 1. Nanostring analyses of baseline (BL) and post-treatment (Post) biopsies from patients participating in MDA 2017-1033 CCOLA trial. Early PD: Patients with progressive disease (PD) prior to randomization, (BL n=29; Post n=10); OBS – 12m: Patients randomized to observation and with PD within 12 months (BL n=14; Post n=8); OBS +12m: Patients randomized to observation and with disease control for ≥ 12 months (BL n=3; Post n=2); Rand – 12m: Patients randomized to olaparib and with PD within 12 months (BL n=23; Post n=18; Rand + 12m: Patients randomized to olaparib with disease control for ≥ 12 months (BL n=10; Post n=6).

Based on these data, we decided to conduct scRNAseq (leveraging funds from other sources) of paired Biopsy 1 and Biopsy 2 samples to inform markers of interest to evaluate by mIF (see below).

5. SINGLE-CELL RNA SEQUENCING. Note: Funding not included in this award.

Milestone 1. Complete interim analysis of sc-RNA-seq

- Expected, 09/2021, revised 06/2024

In Y3Q3, we identified 50 patients with candidate biopsy sets for analysis (Biopsy 1, n=49; Biopsy 2, n=40) from bone (n=22), liver (n=8), lymph nodes (n=19) and prostate (n=1). Following cell count and viability analyses, paired samples from 10 patients (n=20) were selected to proceed to scRNAseq (Figs. 2 and 3). Five patients reached randomization, but the other five progressed while receiving chemotherapy.

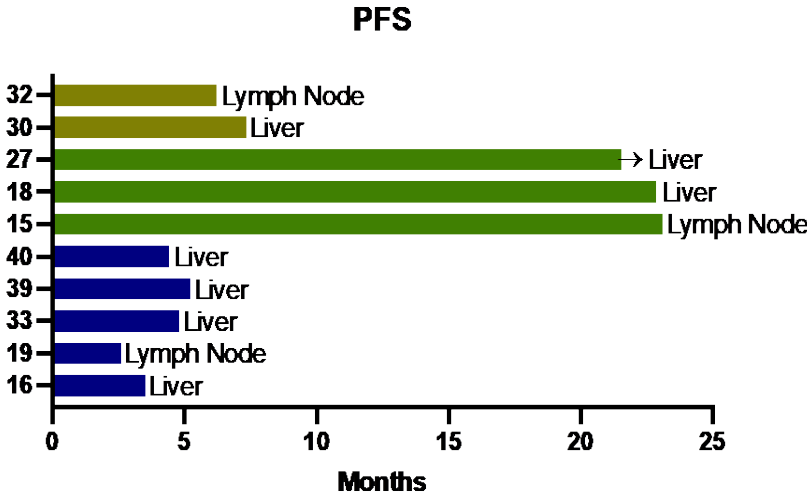


Figure 2. Progression free survival (PFS) of patients with scRNAseq data for Biopsy 1 and Biopsy 2 samples. Depicted in green are the patients that reached randomization. Depicted in blue are the patients that progressed on chemotherapy. The arrow indicates the patient remains on study treatment.

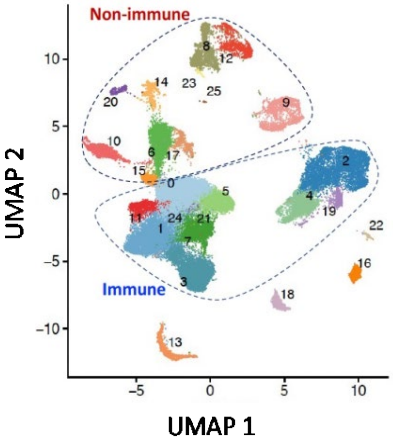


Figure 3. UMAP Umap plot of 48,542 cells from paired samples (n=20) from 10 trial participants. Liver, n=14; Lymph nodes, n=6.

Preliminary data suggested that contrary to previous reports in prostate cancer, the post-chemotherapy samples contained a higher proportion of T cells than myeloid cells (Figs. 4 and 5), suggesting that chemotherapy may cause a T cell infiltration and/or myeloid cell depletion. Alternatively, it is possible that aggressive variant prostate cancers have a distinct immune TME, enriched in T cells, to begin with.

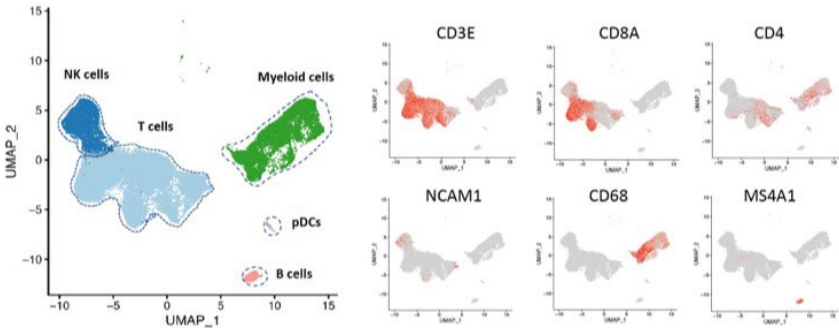


Figure 4. UMAP showing major immune cells in the metastatic AVPC TME.

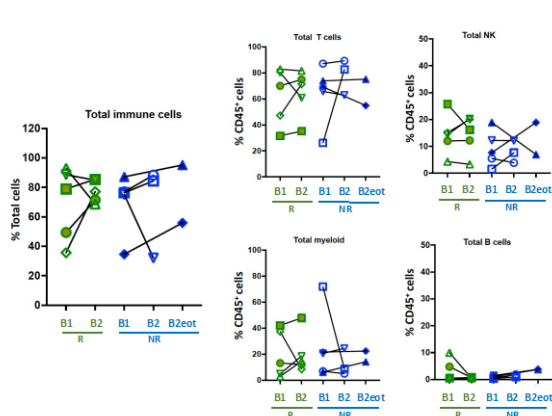


Figure 5. Changes in major immune cells with the addition of cetrelimab (α -PD1) to cabazitaxel carboplatin chemotherapy in AVPC tumors. (B1, biopsy #1 obtained after 1 cycle of chemotherapy; B2, biopsy #2 obtained after the addition of cetrelimab to 2 additional cycles of chemotherapy (i.e. after 3 cycles of chemotherapy and 2 of cetrelimab); B2eot: biopsy #2 obtained when the patient demonstrated evidence of progressive disease; R, responder; NR, non responder.)

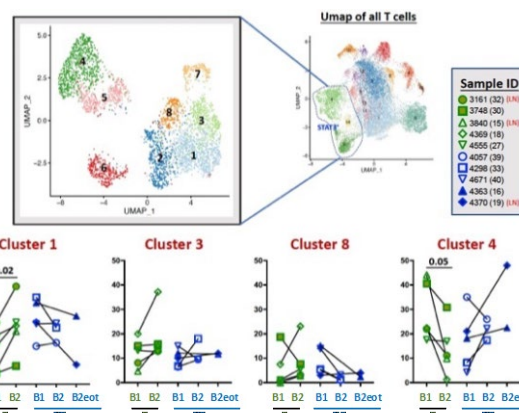


Figure 6. Changes in T cell subpopulations with the addition of cetrelimab (α -PD1) to cabazitaxel carboplatin chemotherapy in AVPC tumors. (B1, biopsy #1 obtained after 1 cycle of chemotherapy; B2, biopsy #2 obtained after the addition of cetrelimab to 2 additional cycles of chemotherapy (i.e. after 3 cycles of chemotherapy and 2 of cetrelimab); B2eot: biopsy #2 obtained when the patient demonstrated evidence of progressive disease; R, responder; NR, non responder.)

To address these questions, we amended the trial to request consent from participating patients to undergo an optional image-guided tumor biopsy prior to the start of chemotherapy (Biopsy #0 above).

In addition, more detailed analyses indicated that the effect of PD1 on each of the immune cell types is distinct between responders and non-responders (Fig. 6).

Once we have assembled a complete set of Biopsy #0, #1 and #2 from ≥ 10 patients ($\sim$ half responders and half non-responders) with adequate cell counts and viabilities, we will subject these to scRNAseq and, from there, select the markers for analysis by mIF.

Analysis of Biopsy #3 sets (to compare tumors treated with niraparib vs niraparib-cetrelimab) will take place once biopsy assembly has been completed.

Milestone 2. Complete scRNA-seq and interpretation

- Expected 03/2024, revised 12/2024, as above.

6. DATA ANALYSIS, DISSEMINATION AND MANUSCRIPT PREPARATION

Milestone 1. Complete assembly of clinical data

- Expected, 12/2023, revised 09/2024, given delayed accrual due to COVID19. Note that improvements in our database Prometheus, allow for greater efficiency in assembly of clinical trial data, such that assembly of clinical data can occur in real time. Thus, the period required to assemble the clinical data can be significantly shortened.
- Pending trial completion

Milestone 2. Complete statistical analysis of clinical endpoints

- Expected 03/2024, revised 12/2024
- Pending trial completion

Milestone 3. *Integrate clinical and correlative data*

- **Expected, 06/2024, revised 12/2024**
- Pending trial completion

Milestone 4. *Report of findings in abstract form*

- **Expected, 07/2024, revised 01/2025**
- Pending trial completion

Milestone 5. *Final report*

- **Expected 09/2024, revised 03/2025**
- Pending trial completion

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Accrual and biopsy collection has continued as planned. Of the 93 eligible patients, **26 remain on treatment** (14 remain on induction chemoimmunotherapy and 12 on maintenance treatment), **28 are in follow up** and **39 are off study** (37 have passed away, 1 withdrew consent after a concurrent diagnosis of glioblastoma and another after deciding they did not want to return for treatment). Forty patients ended study treatment during induction chemoimmunotherapy, 27 after randomization. **Twelve** patients ended treatment on study for reasons other than progression:

- 5 patients received only cycle #1 of carboplatin and cabazitaxel:
 - 1 ended study participation and withdrew consent because he was diagnosed with a concurrent glioblastoma.
 - 1 died 8 days after cycle #1 of chemotherapy, reportedly from a myocardial infarction.
 - 1 developed sepsis and multiorgan failure after cycle #1 of chemotherapy.
 - 1 decided ended study participation after cycle #1 of chemotherapy given travel burden.
 - 1 attempted suicide after cycle #1 of chemotherapy.
- 3 patients were taken off study treatment during the induction phase for reasons other than disease progression.
 - 1 developed hemophagocytic lymphohistiocytosis deemed to be likely secondary to EBV with or without association to cetrelimab.
 - 1 was hospitalized for diverticulitis with perforation after cycle #3 of chemoimmunotherapy.
 - 1 died from neutropenic sepsis after cycle #4 of chemoimmunotherapy.
- 4 patients stopped treatment after randomization.
 - 2 patients ended study participation in the absence of PD to receive Pluvicto locally.
 - 1 patient ended study participation after developing lung infiltrates possibly related to treatment vs infection.
 - 1 patient who was found to have MSI-high disease after starting study treatment, ended study participation after randomization to arm A (niraparib alone).

(One patient previously reported to have come off study treatment in the absence of PD due to a suicide attempt, did in fact have symptomatic PD, so he has been removed from this list.)

No other unexpected adverse events have been reported to date.

Forty patients have been randomized to date, 19 to niraparib alone and 21 to niraparib plus cetrelimab.

As detailed above, 166 biopsies have been assembled to date (n=7 optional pre-chemotherapy; n=76 post-cycle#1; n=57 post-cycle #3; n=20 post-cycle #9; n=6 optional end-of-treatment).

Preliminary scRNAseq data has been generated to inform mIF assays.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period, we will complete accrual and tumor biopsy assembly. We expect to also complete mIF analyses based on scRNAseq data from selected samples.

4. IMPACT

Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

It is remarkable that 12 (21%) of the 57 patients registered between 01/2021 and 07/2022 have demonstrated PFS $\geq$ 12 months (5 ongoing and 4 close to or up to 2 years), a rare occurrence in patients meeting AVPC criteria in previous clinical trials.

Our preliminary scRNAseq data has also revealed remarkable differences in the immune TME between responders and non-responders to treatment. These will be key data to identify resistance mechanisms and inform treatment combinations that can overcome them.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Taxane-platinum combinations with or without PD1 blockade are used in a number of malignancies. Our data will contribute to the understanding of resistance mechanisms and inform future combinations in these tumors as well.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. CHANGES/PROBLEMS

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

We amended the trial to include an optional pre-chemotherapy biopsy (Biopsy #0) to determine whether the increased proportion of T cells relative to myeloid cells that we observed in the TME is due to the AVPC phenotype or to the effect of chemotherapy.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Our accrual has decreased to an average of 3 patients/month in the last reporting period. This may be explained because the research nurse assigned to the trial was slow in responding to referrals. The study team has changed and in 08/2023 (typically a low accrual month due to the summer break) was 6. Although we have adjusted our timelines to reflect the 3 patients/month, our hope is that, with the new team, we will complete accrual earlier than stated.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

As detailed above, we amended the trial to include an optional pre-chemotherapy biopsy (Biopsy #0). Because we had budgeted for all patients to undergo 3 biopsies, and due to progression and other causes (e.g. tumor shrinkage) not all patients are undergoing all 3 biopsies, there is sufficient budget to cover Biopsy #0 in the remaining patients that consent to it.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

As detailed above, we amended the trial to include an optional pre-chemotherapy biopsy (Biopsy #0).

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS

List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

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

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- data or databases;
- physical collections;
- audio or video products;
- software;
- models;
- educational aids or curricula;
- instruments or equipment;
- research material (e.g., Germplasm; cell lines, DNA probes, animal models);
- clinical interventions;
- new business creation; and
- other.

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".

Example:

Name:	Mary Smith
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	1234567
Nearest person month worked:	5
Contribution to Project:	Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support:	The Ford Foundation (Complete only if the funding support is provided from other than this award.)

The personnel who worked on this project on **Year 3 (9/1/2022 to 8/31/2023)** are the following:

Name:	Ana Aparicio
Project Role:	Principal Investigator
Research Identifier (e.g. ORCID ID):	000-0003-0900-0923
Nearest Person Months Worked:	1 calendar month
Contribution to Project:	Dr. Aparicio supervises all aspects of the proposed work and leads the clinical study.
Funding Support:	N/A

Name:	James P. Long
Project Role:	Statistician
Research Identifier (e.g. ORCID ID):	0000-0001-5853-5938
Nearest Person Months Worked:	1 calendar month

Contribution to Project:	Dr. Long supervises the monitoring of the trial, as well as the statistical analysis of the clinical trial outcomes and that of the correlative data.
Funding Support:	N/A

Name:	Miao Zhang
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	0000-0003-4912-2570
Nearest Person Months Worked:	1 calendar month
Contribution to Project:	Dr. Zhang serves as the Pathologist in this proposal. She evaluates the tumor content of the image-guided biopsies and touch preparations, as well as analyzes the results of the IF and aid in their interpretation.
Funding Support:	N/A

Name:	Rebecca Slack Tidwell
Project Role:	Sr. Statistical Analyst
Research Identifier (e.g. ORCID ID):	0000-0003-3041-8582
Nearest Person Months Worked:	1 calendar month
Contribution to Project:	She has contributed the statistical design of this proposal and will assist in the statistical analysis of the clinical trial outcomes, as well as the correlative data, for interpretation and publication.
Funding Support:	N/A

Name:	Elizabeth Martinez
Project Role:	Data Manager
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	2 calendar months
Contribution to Project:	Ms. Martinez replaced Rachel Randall as Data Manager. She is responsible for monitoring the assembly and distribution of biological samples obtained from study participants, coordination of data analysis and integration, generation of data figures and tables for presentation.
Funding Support:	N/A

Name:	Terri DeHoyos
Project Role:	Regulatory Oversight Coordinator
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	1 calendar month (for one month: 9/2022-10/2022)
Contribution to Project:	Ms. DeHoyos worked with the Trial Oversight Coordinator to maintain the schedule of communications with regulatory agencies and was responsible for the submission of the required documentation to such agencies. This includes submission of any required amendments and supervision of appropriate filing of all required regulatory documentation. Ms DeHoyos left the department on 10/15/2022.

Funding Support:	N/A
-------------------------	-----

Name:	Yuko Yamamura
Project Role:	Regulatory Oversight Coordinator
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	1 calendar month (for one month: 10/2022-11/2022)
Contribution to Project:	Ms. Yamamura assumed DeHoyos responsibilities in this grant until a new Regulatory Oversight Coordinator was found. She worked with the Trial Oversight Coordinator to maintain the schedule of communications with regulatory agencies and was responsible for the submission of the required documentation to such agencies. This includes submission of any required amendments and supervision of appropriate filing of all required regulatory documentation.
Funding Support:	N/A

Name:	Marium Kaukab
Project Role:	Regulatory Oversight Coordinator
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	1 calendar month (effective 11/16/2022)
Contribution to Project:	Ms. Kaukab assumed the responsibilities of the Regulatory Oversight Coordinator. She worked with the Trial Oversight Coordinator to maintain the schedule of communications with regulatory agencies and was responsible for the submission of the required documentation to such agencies. This includes submission of any required amendments and supervision of appropriate filing of all required regulatory documentation.
Funding Support:	N/A

Name:	Miguel Socop
Project Role:	Tissue Procurement Specialist
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	1 calendar month
Contribution to Project:	He is responsible for the collection, procurement and harvest of fresh biological specimens mandated during study conduct and requested (optional) at end of treatment; facilitating specialized harvests for investigators; and processing, archiving and distribution of routine specimens banked for future use. She also assists in the reconciliation and organization of data and records for timely submission of reports on the procured human tissues.
Funding Support:	N/A

Name:	Collin Wehunt
Project Role:	Research Nurse
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	6 calendar months (for 9 months, left department 5/31/2023)

Contribution to Project:	Collin assisted Dr. Aparicio with the screening and follow up of patients.
Funding Support:	N/A

Name:	Kareema Scott
Project Role:	Research Nurse
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	6 calendar months (for 3 months)
Contribution to Project:	Ms. Scott replaced Collin Wehunt as Research Nurse effective 7/17/2023. She assists Dr. Aparicio with the screening and follow up of patients.
Funding Support:	N/A

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

Yes

If there is nothing significant to report during this reporting period, state "Nothing to Report." If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. 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.

APARICIO, Ana

CURRENT

(NEW)

FPI7824

(Frigo)

Title:

Targeting Arginine Metabolism to Treat Aggressive Variant Prostate Cancers

Time Commitments:

0.24 calendar months (2% effort)

Supporting Agency:

Mike Slive Foundation

Grant Officer:

Emily Capilouto, emily@mikeslivefoundation.org

Performance Period:

01/01/2023-12/31/2023

Level of Funding:

Total

Goal(s):

To discover additional tumor characteristics that can improve the predictive value of the AVPC criteria and advise therapeutic interventions to improve clinical outcomes.

Specific Aims:

- 1. Determine the distribution of urea cycle enzymes across the AVPC tumor microenvironment.*
- 2. Test the effects of ADI-PEG20 + carboplatin + cabazitaxel in preclinical models of AVPC.*

Role:

Co-PI

Overlap:

None

NCT02703623

(Aparicio)

Title:

2014-0386: A Dynamic Allocation Modular Sequential Trial of Approved and Promising Therapies in Men with Metastatic Castrate Resistant Prostate Cancer

Time Commitments:

0.12 calendar months (1% effort)

Supporting Agency:	Janssen Pharmaceuticals Inc.
Grant Officer:	Not available
Performance Period:	05/03/2016-05/02/2024
Level of Funding:	
Goal(s):	This phase II trial studies the side effects and how well abiraterone acetate, prednisone, and apalutamide work with or without ipilimumab or cabazitaxel and carboplatin in treating patients with castration-resistant prostate cancer that has spread to other places in the body.
Specific Aims:	1. Estimate the overall survival (OS) of men with metastatic castration-resistant prostate cancer (mCRPC) who have satisfactory features after to 8 weeks of maximal androgen receptor (AR)-inhibitory therapy and receive treatment with abiraterone acetate, prednisone and apalutamide plus or minus ipilimumab. 2. Estimate the OS of men with mCRPC who have unsatisfactory features after to up to 8 weeks of maximal AR-inhibitory therapy and receive treatment with abiraterone acetate, prednisone, apalutamide, cabazitaxel and carboplatin. 3. Determine the toxicity profile of the following combinations in men with mCRPC: a. Abiraterone acetate, prednisone, apalutamide. b. Abiraterone acetate, prednisone, apalutamide and ipilimumab. c. Abiraterone acetate, prednisone, apalutamide, cabazitaxel and carboplatin. 4. Determine whether the baseline "AR response signature" correlates with satisfactory or unsatisfactory features after up to 8-weeks of treatment with abiraterone, prednisone and apalutamide.
Overlap:	None
NCT03263650	(Aparicio)
Title	2017-0133: Randomized Phase II Study of Olaparib Maintenance Following Cabazitaxel-Carboplatin Induction Chemotherapy in Men with Aggressive Variant Prostate Cancer (AVPC)
Time Commitments:	0.12 calendar month (1% effort)
Supporting Agency:	AstraZeneca
Grant Officer:	Gayle Ewing, Gayle.Ewing@astrazeneca.com
Performance Period:	08/15/2017-08/14/2024
Level of Funding:	
Goal(s):	The goal of this study is to learn if olaparib, when given after treatment with cabazitaxel, carboplatin, and prednisone, can help to control aggressive variant prostate cancer (AVPC). The safety of these drugs will also be studied.
Specific Aims:	n/a
Overlap:	None
(THIS AWARD)	
W81XWH-20-10257	(Aparicio)
Title:	PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)
Time Commitments:	1.20 calendar months (10% effort)
Supporting Agency:	DOD
Grants Officer:	Kenneth E. Grenier, kenneth.e.grenier2.civ@mail.mil

Performance Period:	09/01/2020-08/31/2024
Level of Funding:	
Goal(s):	Our overall goal is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.
Specific Aims:	1. Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC. 2. Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.
Overlap:	None

<i>W81XWH-21-1-0522</i>	<i>(Wang)</i>
Title:	<i>PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer</i>
Time Commitments:	0.60 calendar months (5% effort)
Supporting Agency:	DOD
Grants Officer:	Kimberly Carter, Kimberly.m.carter47.civ@mail.mil
Performance Period:	09/01/2021-08/31/2024
Level of Funding:	Our overall goal is to develop combination therapy to improve the clinical outcome of platinum-taxane chemotherapy in patients with NEPC.
Goal(s):	
Specific Aims:	1. Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs. 2. Examine the mechanism(s) by which KDM4A regulates UPR signaling. 3. Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.
Role:	Co-Investigator
Overlap:	None

(NEW)	
<i>22CHAL09</i>	<i>(Zhao)</i>
Title:	<i>Targeting B7-H3 in Aggressive Variant Prostate Cancer</i>
Time Commitments:	1.20 calendar months (10% effort)
Supporting Agency:	Prostate Cancer Foundation
Grants Officer:	Audrey Gardner, applications@pcf.org
Performance Period:	01/23/2023-01/22/2025
Level of Funding:	
Goal(s):	Our overall goal is to determine the therapeutic potential of DS-7300, a B7-H3-targeting antibody-drug conjugate (ADC) warheaded with a novel DNA topoisomerase inhibitor, in men with AVPC.
Specific Aims:	1. Determine the differential expression patterns of B7-H3 in molecularly defined mCRPC subsets. 2. Determine regulatory mechanisms of B7-H3 expression by AVPC molecular profile in mCRPC. 3. Evaluate the efficacy of DS-7300 in preclinical models of AVPC
Role:	Co-PD/PI
Overlap:	None

(NEW)

W81XWH-22-1-0259

(Aparicio)

Title:

PC210079P1: An Integrated Genomic Definition and Therapeutic Strategy for Androgen Indifferent Prostate Cancers

Time Commitments:

1.80 calendar months (15% effort)

Supporting Agency:

DOD-PCRP-DSA

Grant Officer:

Michelle L. Cromwell, michelle.l.cromwell.civ@mail.mil

Performance Period:

09/30/2022-09/29/2025

Level of Funding:

Goal(s):

To develop statistical methods and tools to further the genomic analysis of heterogeneous tumor samples.

Specific Aims:

1. To develop and validate compartment-specific plasticity scores using integrative deconvolution of bulk genomic and transcriptomic signatures.
2. To determine the association between the plasticity scores, clinical outcomes and clinically available biomarker signatures.

Role:

Partnering PI

Overlap:

None

(NEW)

R01 CA275990-01

(Zhao)

Title:

Novel Approaches Targeting B7-H3 in Castration-Resistant Prostate Cancer

Time Commitments:

0.60 calendar months (5% effort)

Supporting Agency:

NIH/NCI

Grant Officer:

Justin Birken, birkenjg@mail.nih.gov

Performance Period:

01/01/2023-12/31/2027

Level of Funding:

Goal(s):

The overall objective of this application is to elucidate the complex role of B7-H3 signaling in prostate cancer as well as develop biomarker-driven B7-H3 targeted therapy for castration-resistant prostate cancer.

Specific Aims:

1. Elucidate B7-H3's impact on progression of prostate cancer containing PTEN/TP53 loss.
2. Understand how B7-H3 signaling modulates immunosuppressive myeloid cells in CRPC.

Role:

Co-Investigator

Overlap:

None

NCT04702737

(Aparicio)

Title:

2021-0108: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Time Commitments:

0.12 calendar months (1% effort)

Supporting Agency:

Amgen Inc.

Grant Officer:

Shani Hilliard, shilliar@amgen.com

Performance Period:

11/01/2021-10/31/2028

Level of Funding:

Goal(s): The overall goal of this study is to evaluate the safety and tolerability of Tarlatamab and will determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

Aims: N/A

Overlap: None

(NEW)

NCT04428788

Title:

(Aparicio)

2022-0612: A Phase 1, Multi-Center, Open-Label, Dose-Finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Cc-94676 in Subjects with Metastatic Castration-Resistant Prostate Cancer

Time Commitments: 0.12 calendar months (1% effort)

Supporting Agency: Bristol-Myers Squibb

Grant Officer: Jennifer Walsh Jennifer.Walsh1@bms.com

Performance Period: 12/15/2022-12/14/2029

Level of Funding:

Goal(s): The purpose of this study is to assess the safety, tolerability and preliminary efficacy of CC-94676 in men with progressive metastatic castration resistant prostate cancer.

Aims: Primary Objectives: 1. Determine the safety and tolerability of CC-94676. 2. Define the non-tolerated dose (NTD), the maximum tolerated dose (MTD), and/or the recommended Phase 2 dose (RP2D) of CC-94676. Secondary Objectives: 1. Provide information on the preliminary efficacy of CC-94676. 2. Characterize the pharmacokinetics (PK) of CC-94676 in plasma

Overlap: None

PREVIOUS (Recently completed since the last report)

P50 CA140388-10

Title:

(Logothetis/Thompson)

MD Anderson Cancer Center Prostate Cancer SPORE

Project 1: Integrating Ipilimumab Immunotherapy with Approved Treatment Strategies in CRPC

Time Commitments: 0.36 calendar months (3% effort)

Supporting Agency: NIH/NCI

Grants Officer: Ashley Salo, ashley.salo@nih.gov

Performance Period: 09/01/2016-08/31/2023 NCE

Level of Funding:

Goal(s): To rationally integrate anti-CTLA-4 (ipilimumab) immunotherapy with agents targeting the AR signaling pathway to provide durable clinical benefit with improved survival in patients with prostate cancer, and utilize novel imaging techniques to accurately identify tumor responses.

Specific Aims: 1. To identify biological changes indicative of mechanistic pathways that contribute to clinical outcomes in matched tumor and blood specimens obtained from prostate cancer patients given drugs targeting the AR signaling pathway plus anti-CTLA-4 immunotherapy. 2. To determine clinical outcomes after treatment with AR-targeting agents (ARN-509 + abiraterone acetate) followed by concurrent anti-CTLA-4 immunotherapy and prospectively evaluate the effectiveness of selected

biological pathways identified in Aim 1 to be indicative of mechanistic pathways that contribute to clinical outcomes.

3. To determine the efficacy of targeting B7-H3 and B7-H4 with radiolabeled monoclonal antibodies as a non-invasive means to detect prostate cancer.

Role: Co-Investigator, Project 1

Overlap: None

LONG, James

CURRENT

FUND124339

(Li)

Title:

Theranostic Heterodimer Eph-Targeting Peptides for Ovarian & Breast Cancer

Time Commitments: 0.60 calendar months (5% effort)

Supporting Agency: Emerson Collective

Grants Officer: info@mdandersoncollective.com

Performance Period: 10/01/2021-12/16/2023

Level of Funding:

Goal(s):

To lead to new diagnostic and therapeutic agents that have a profound positive impact on the survival of women with these devastating diseases

Specific Aims:

1. Design, develop, and validate stable compounds that home to tumor cells that have EphB4/EphA2 on the cell surface.
2. Assess the PET imaging properties of the 68Ga-labeled lead compounds that yield the clearest images of tumors.
3. Evaluate the antitumor activity of 177Lu-labeled versions of our lead compounds against tumors with EphB4/EphA2 present on the surface of the tumor cells and tumor-associated endothelial cells.

Overlap:

None

5 P30 CA016672-46

(Pisters)

Title:

Cancer Center Support Grant (CCSG)-Biostatistics Resource Group

Time Commitments: 1.20 calendar months (10% effort)

Supporting Agency: NIH/NCI

Grants Officer: Henry P. Ciolino, ciolinoh@mail.nih.gov

Performance Period: 07/01/2019-06/30/2024

Level of Funding:

Goal(s):

To enhance the scientific excellence of research at MD Anderson through outstanding statistical designs and methods, including the proper and efficient use of standard and cutting-edge methods.

Specific Aims:

1. Provide statistical collaboration and consultation services in support of cancer research in laboratory experiments and clinical trials;
2. Play a direct role in the planning and review of clinical protocols;
3. Provide educational programs in biostatistical methods; and
4. Design, develop, distribute, and implement software and database systems to support all the computational needs of cancer researchers.

Role: Biostatistician

Overlap: None

R01 CA231465-05 (Dinney/Kalluri)
 Title: *Rigorous and Reproducible Mutational Analysis of the Urinary Exosomal DNA*
 Time Commitments: 0.60 calendar months (5% effort)
 Supporting Agency: NIH/NCI
 Grants Officer: Matthew R. Young, youngma@mail.nih.gov
 Performance Period: 07/1/2019-06/30/2024
 Level of Funding:
 Goal(s): To test the utility of exoDNA as an analyte, for detection, and monitoring of bladder cancer as well as identification of novel drivers and pathways that contribute to BLCA progression. PID8079
 Specific Aims: 1. Identify procedure(s) to obtain high quality exosomes and maximize exoDNA yield from urine.
 2. Optimize whole genome amplification of serum and urine exoDNA.
 3. Determine computational procedures for rapid and reproducible identification of mutations and biomarkers using exoDNA.
 4. Independent validation of exoDNA analysis in bladder cancer.
 Role: Co-Investigator
 Overlap: None

5 UL1 TR003167-05 (Karp)
 Title: *Center for Clinical and Translational Science*
 Time Commitments: 0.60 calendar months (5% effort)
 Supporting Agency: NIH/NCATS subaward via UT Health Science Center, Houston
 Grants Officer: Carol Merchant, merchantc@mail.nih.gov
 Performance Period: 07/24/2019-06/30/2024
 Level of Funding:
 Goal(s): This program advances clinical and translational science and maximizes the speed at which novel treats can be brought to patients to improve outcomes and quality of life.
 Specific Aims: 1. Provide our investigators, staff, trainees, and scholars with the skills and knowledge necessary to advance discoveries and their translation in the new environment of clinical and translational research (Workforce Development).
 2. Collaborate with all of our stakeholders in a mutually beneficial way to advance translation by furthering engagement and team science (Collaboration/Engagement).
 3. Integrate pediatric and geriatric patients, Hispanic patients with cancer, and the LGBTQ+ community into the full spectrum of clinical and translational research (Integration).
 4. Advance translational science by providing novel processes, increasing efficiency, and streamlining research (Methods/Processes).
 5. Create and apply innovative informatics solutions to advance translational research, train the CTSA workforce, disseminate best practices, engage communities and integrate clinical and basic research data (Informatics).
 Role: Collaborator
 Overlap: None

(THIS AWARD)

W81XWH-20-1-0257

Title:

(Aparicio)

PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)

Time Commitments:

0.60 calendar months (5% effort)

Supporting Agency:

Department of Defense (DOD)

Grants Officer:

Kenneth E. Grenier, kenneth.e.grenier2.civ@mail.mil

Performance Period:

09/01/2020-08/31/2024

Level of Funding:

The overall goal is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.

Goal(s):

Specific Aims:

1. Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC.
2. Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.

Role:

Statistician

Overlap:

None

W81XWH-21-1-0559

Title:

(Wang X)

RA200128: Enhancing Axl-Targeted Therapy in Inflammatory Breast Cancer

Time Commitments:

0.72 calendar months (6% effort)

Supporting Agency:

DOD

Grants Officer:

Not available

Performance Period:

07/01/2021-09/14/2024

Level of Funding:

Goal(s):

To develop a novel Axl-targeted therapy for patients with IBC by modulating the immunological status of the TME

Specific Aims:

1. Determine the mechanism of how Axl signaling promotes an immunosuppressive TME in IBC.
2. Establish effective combination approaches targeting the Axl/TBK1 axis in IBC

Role:

Co-Investigator

Overlap:

None

R01 DE029590-04

Title:

(Gillenwater)

Precision Optical Guidance for Oral Biopsy Based on Next-Generation Hallmarks of Cancer

Time Commitments:

0.30 calendar months (2.5% effort)

Supporting Agency:

NIH/NIDCR Subaward Rice University

Grants Officer:

Amanda Melillo, amanda.melillo@nih.gov

Performance Period:

02/25/2020-01/31/2025

Level of Funding:

Goal(s):

To develop and validate a multimodal Active Biopsy Guidance imaging system that provides precise biopsy guidance for detection of oral neoplasia based on the next generation of hallmarks of cancer. (Effort effective 9/1/2020) PID11276

Specific Aims: 1. Develop a compact optical mapping scope that uses Digital Light Processing (DLP) technology to image tissue autofluorescence and actively project a map onto the tissue that highlights areas at high risk for oral neoplasia based on loss of collagen autofluorescence and alterations in epithelial cell NAD(P)H and FAD.
2. Develop a low-cost high resolution probe that can image epithelial cell nuclei, inflammatory cell infiltrate, and subsurface angiogenesis in oral mucosa in vivo with high resolution and high image contrast.
3. Develop a multimodal Active Biopsy Guidance imaging system by integrating the optical mapping scope and the high resolution probe into a single, compact system. The optical mapping scope will highlight areas at risk for neoplasia, automatically projecting a risk map onto the tissue; the high resolution probe will enable high-resolution imaging within high-risk areas to precisely determine when and where to biopsy tissue at risk for neoplasia based on the next generation hallmarks of cancer.
4. Validate the ability of the fully developed Active Biopsy Guidance imaging system to provide real-time precise guidance for selection of oral biopsy sites based on severity score maps developed using the next-generation hallmarks of cancer in high-risk patients undergoing surveillance for oral cancer.

Role: Biostatistician
Overlap: None

RP220051 (Li)
Title: *IRE-based Rational Combination for Effective PDAC Immunotherapy*
Time Commitments: 0.60 calendar months (5% effort)
Supporting Agency: Cancer Prevention & Research Institute of Texas (CPRIT)
Grants Officer: Patty Moore, 512-463-3190, pmoore@cprit.texas.gov
Performance Period: 03/01/2022-02/28/2025
Level of Funding:
Goal(s):

We hypothesize that attenuation of the immunosuppressive TME by depletion of MDSCs or pharmacological modulation of tumor stroma by M-CPA/PTX potentiates IRE + anti-PD-1 to further prolong overall survival and increase the rate of durable response.

Specific Aims: 1. Determine the extent to which therapy directed at CXCR2+ MDSCs potentiate IRE + anti-PD-1.
2. Determine the extent to which M-CPA/PTX directed at immunosuppressive TME potentiate IRE + anti-PD-1.

Role: Collaborator
Overlap: None

(NEW)
W81XWH-22-1-0973 (Futreal)
Title: *Delineating Germline, Tumor and Extrinsic Factors Driving Mucosal Melanoma Risk and Response*
Time Commitments: 0.513 calendar months (4.276% effort)
Supporting Agency: US Department of Defense
Grants Officer: Not available
Performance Period: 09/01/2022-08/31/2025

Level of Funding:
Goals: We will determine the role of genetics in increasing the risk of mucosal melanoma by looking at the constitutional DNA of patients for gene mutations that are likely to have been involved in cancer development, and develop a deep understanding of response to immune therapies.

Specific Aims: 1. To determine the contribution of germline susceptibility alleles to mucosal melanoma risk and implications for clinical translation.
2. To determine the interplay of molecular variation, gut and tumor microbiome, and modifiable host factors on risk of mucosal melanoma progression and therapeutic response.

Role: Co-Investigator
Overlap: None

R01 CA258226-03
Title: *(Genovese)*
Investigation of the Role of Epithelial-Mesenchymal Plasticity in Renal Cell Carcinoma

Time Commitments: 0.60 calendar months (5% effort) – **Effort in Year 5 only**
Supporting Agency: NIH/NCI
Grants Officer: Christopher Hatch, ch29v@nih.gov
Performance Period: 04/01/2021-03/31/2026
Level of Funding:
Goal(s): The goal of this project is to explore the molecular and genetic routes to disease progression, metastatic dissemination and response to therapy

Specific Aims: 1. Characterize subpopulation dynamics during cancer progression and track the fate of mesenchymal cells in the primary tumor, at metastatic sites, and in response to targeted therapy and immune therapy in models of Vhl-driven and Nf2-driven RCC. The relative contribution of genetically engineered events to the emergence of sarcomatoid features will also be assessed.
2. Perform a cross species analysis of genomic and molecular determinants of cell plasticity and lineage evolution. Furthermore, single-cell transcriptomic analysis of cell populations will provide: (i) mechanisms of clonal diversification and evolution in the epithelial and mesenchymal compartment and (ii) putative genetic drivers priming pre-malignant/malignant cells to gain mesenchymal features.
3. Characterize the landscape of context-specific vulnerabilities that define mesenchymal and epithelial cell states through a genome-wide CRISPR-Cpf1-based screening approach.

Role: Biostatistician
Overlap: None

U01 CA239522-03
Title: *(Schmidt)*
Longitudinal Proteomic and Metabolomic Predictors of Pancreatic Cyst Malignant Progression and Early Stage Pancreatic Cancer

Time Commitments: 0.60 calendar months (5% effort)
Supporting Agency: NIH/NCI subaward via Indiana University
Grants Officer: Claire Zhu, cz63u@nih.gov
Performance Period: 04/01/2021-03/31/2026
Level of Funding:

Goal(s): To identify and validate protein and metabolite signatures and their longitudinal changes which can discriminate IPMN malignant progression and detect early-stage PDAC.

Specific Aims: 1. Investigate plasma and cyst fluid levels and trajectories of proteomic biomarkers and metabo-lomics signatures for prediction of IPMN malignant progression in a prospective surveillance cohort.
2. Evaluate levels and trajectories of plasma proteomic biomarkers and metabolomics signatures for detection of early-stage PDAC in a PRoBE-compliant case-control study nested in the PLCO cohort.

Role: Co-Investigator

Overlap: None

R01 CA252729-03

(Kalluri)

Title:

Mechanisms Associated with Organotropic Metastasis

Time Commitments:

0.60 calendar months (5% effort)

Supporting Agency:

NIH/NCI

Grants Officer:

Christopher L. Hatch, ch29v@nih.gov

Performance Period:

07/01/2021-06/30/2026

Level of Funding:

Goal(s):

The central hypothesis of this proposal is that vascular heterogeneity functionally contributes to organotropic metastasis.

Specific Aims:

1. Determine the impact of organ fibrosis on the tropism of breast cancer metastasis.
2. Investigate the mechanism of Ang-2 mediated organ specific vascular disruption to facilitate tropic metastasis.
3. Examine the functional contribution of claudin-5 in lung metastasis.

Role:

Co-Investigator

Overlap:

None

(NEW)

R01 CA257842-01A1

(Li)

Title:

Pre-IND Development of Polymeric Micelles with Dual Drug Payloads for HCC Therapy

Time Commitments:

0.60 calendar months (5% effort)

Supporting Agency:

NIH/NCI

Grants Officer:

Jeanette Marketon, jeanette.marketon@nih.gov

Performance Period:

08/01/2022-06/30/2026

Level of Funding:

Goals:

The major goals of the proposed project are to de-risk clinical translation of M-CPA/PTX and to obtain a robust IND (investigative new drug) package.

Specific Aims:

1. To scale up synthesis of high-quality M-CPA/PTX and fully characterize the resulting products.
2. To determine the antitumor efficacy, biodistribution, pharmacokinetics (PK), toxicity, pharmacodynamics (PD), and PK/PD correlation of M-CPA/PTX in preclinical models of HCC.
3. To evaluate the mechanism by which M-CPA/PTX exerts its anti-HCC activity.

Role:

Co-Investigator

Overlap:

None

R01 CA258540-02

Title:

(Li and Wang)

Development of Irreversible Electroporation Based Rational Combinations to Potentiate the Activity of Cancer Immunotherapy Against Pancreatic Ductal Adenocarcinoma

Time Commitments: 0.60 calendar months (5% effort)

Supporting Agency: NIH/NCI

Grants Officer: Mehrdad Mohseni, mohsenim@csr.nih.gov

Performance Period: 09/01/2021-08/31/2026

Level of Funding:

Goal(s):

We hypothesize that attenuation of the immunosuppressive TME by depletion of MDSCs or suppression of glutaminolysis by Re-Phen potentiates IRE+ICB to further prolong overall survival and increase the rate of durable response.

Specific Aims:

1. To identify immunosuppressive factors associated with long-term versus short-term response to IRE+ICB. We will use CyTOF immune profiling, scRNAseq, and cytokine array analyses to fully characterize the impact of IRE in the presence and absence of anti-PD-1 on the immunosuppressive TME.
2. To determine the extent to which therapies directed at MDSCs potentiate IRE+ICB therapy.
3. To determine the extent to which disruption of the metabolic program by theranostics agent Re-Phen potentiates IRE+ICB. The findings from this project are expected to reveal previously undefined roles of MDSCs and deregulated metabolic programming in immune suppression in the context of combined IRE + ICB therapy.

Role:

Co-Investigator

Overlap:

None

(NEW)

Title:

A Phase II Study to Evaluate the Efficacy and Safety of Pembrolizumab in Combination with Mitotane in Patients with Advanced Adrenocortical Carcinoma

Time Commitments: 1.20 calendar months (10% effort)

Supporting Agency: The University of Texas MD Anderson Cancer Center

Grants Officer: Not available

Performance Period: 05/01/2022-04/30/2027

Level of Funding:

Goal(s):

Assess the clinical efficacy of the combined use of MT with PEM in patients with advanced ACC. Evaluate the safety and efficacy of the combined use of MT plus PEM in patients with advanced ACC. Correlate safety and efficacy data with steroid profile, immune markers and MT levels.

Specific Aims:

1. Assess the clinical efficacy of the combined use of MT with PEM in patients with advanced ACC.
2. Evaluate the safety and efficacy of the combined use of MT plus PEM in patients with advanced ACC.
3. Correlate safety and efficacy data with steroid profile, immune markers and MT levels.

Overlap:

None

(NEW)

R01 DE032051-02

(Gillenwater)

Title:

Deep Learning Microscope for Slide-Free and Digital Histology

Time Commitments:

0.36 calendar months (3% effort)

Supporting Agency:

NIH/NIDCR-William Marsh Rice University

Grants Officer:

Noffisat Oki, noffisat.oki@nih.gov

Performance Period:

07/12/2022-06/30/2027

Level of Funding:

Goals:

The goal of this proposal is to develop and validate the DeepDOF platform for rapid, slide-free, digital histology of freshly resected tissue specimens.

Specific Aims:

1. Develop the DeepDOF platform for rapid, subcellular imaging of freshly resected tissue samples.
2. Carry out a clinical evaluation of DeepDOF to determine its ability to assess oral tumor margin status immediately following surgery.
3. Develop a machine learning framework to identify positive margins in and assist annotation of large-area, cellular-resolution maps of oral surgical specimens.

Role:

Co-Investigator

Overlap:

None

(NEW)

R37 CA272744-02

(Yao)

Title:

Targeting Acquired Resistance in KRAS Driven Cancers

Time Commitments:

0.36 calendar months (3% effort)

Supporting Agency:

NIH/NCI

Grants Officer:

Suzanne L. Forry, forryscs@mail.nih.gov

Performance Period:

08/12/2022-07/31/2027

Level of Funding:

Goals:

The goal is to reveal SDC1 as a potential therapeutic target against KRAS mutated cancers.

Specific Aims:

1. Delineate the molecular mechanisms underlying SDC1-mediated bypass of KRAS-dependence.
2. Characterize the regulation of SDC1 membrane localization in tumor cells with KRAS targeted therapy.
3. Determine the potential of targeting SDC1 and oncogenic KRAS in vivo.

Role:

Co-Investigator

Overlap:

None

PREVIOUS (Recently completed since the last report)

Emerson Award

(Wang)

Title:

Enhancing EGFR-Targeted Therapy by Blocking Immunosuppression in the Tumor Microenvironment in Inflammatory Breast Cancer

Time Commitments:

0.54 calendar months (4.5% effort)

Supporting Agency:

Emerson Collective

Grants Officer:

Not available for this submission

Performance Period:

03/02/2020-10/31/2022

Level of Funding:

Goal(s): To identify critical molecules and related mechanisms that contribute to panitumumab-induced immune response in IBC. (Effort effective 12/1/2020)

Specific Aims: 1. Identify chemokines that are regulated by the EGFR pathway and contribute to IBC aggressiveness.
2. Determine the role of chemokines in the EGFR-modulated immune response in a humanized IBC mouse model.

Role: Collaborator

Overlap: None

P50 CA140388-10 (Logothetis/Thompson)
Title: MD Anderson Cancer Center Prostate Cancer SPORE. Core 1: Biostatistics Core

Time Commitments: 0.12 calendar months (1% effort, unsalaried)

Supporting Agency: NIH/NCI

Grants Officer: Ashley Salo, ashley.salo@nih.gov

Performance Period: 09/01/2016-08/31/2023 NCE

Level of Funding:

Goal(s): The Biostatistics and Bioinformatics Core provides comprehensive biostatistic and bioinformatic expertise to ensure statistical integrity and optimize data analysis for the studies in the SPORE.

Specific Aims: 1. Provide guidance in the design and conduct of clinical trials and other experiments (including high-dimensional genomic and proteomic studies) that arise from the ongoing research of the SPORE.
2. Provide innovative and tailored statistical modeling, simulation techniques, and data analyses as needed for the main projects, developmental research and career development projects, and other cores to achieve their specific aims.
3. Ensure that the results of all projects are based on well-designed experiments and are appropriately interpreted.
4. Provide guidance in the design and use of an information system to store appropriate data generated by all projects; develop integrated computational libraries and tools for producing documented, reproducible statistical and bioinformatics analyses; and support the use of these tools for analyses conducted by and on behalf of the projects.

Role: Co-Investigator

Overlap: None

P50 CA127001-12 (Lang)
Title: SPORE in Brain Cancer

Time Commitments: 1.20 calendar months (10% effort)

Supporting Agency: NIH/NCI

Grants Officer: Leah Hubbard, leah.hubbard@nih.gov

Performance Period: 09/01/2019-08/31/2023

Level of Funding:

Goal(s): To conduct cutting-edge translational research for the prevention and treatment of brain cancer.

Specific Aims: 1. Provide biostatistics and bioinformatics expertise in the design and conduct of laboratory experiments and clinical trials arising from the research proposed in this application.
2. Provide biostatistics and bioinformatics analysis and interpretation of all data collected under the SPOR Projects, Developmental Projects, and other Cores.
3. Collaborate and assist all project investigators with the publication of scientific results.

Role: Co-Investigator

Overlap: None

R01 CA258523-01A1 (Ueno)
Title: *Development of a Novel Therapy Targeting the Tumor Microenvironment in Inflammatory Breast Cancer*

Time Commitments: 0.60 calendar months (5% effort)

Supporting Agency: NIH/NCI

Grants Officer: Christopher L. Hatch, ch29v@nih.gov

Performance Period: 03/01/2022-02/28/2027

Level of Funding:

Goal(s): To enhance the efficacy of immunotherapy in IBC patients by modulating the TME through EGFR inhibition.

Specific Aims: 1. Determine how the EGFR pathway promotes IBC tumor growth by modulating the TME in IBC.
2. Determine clinical relevance of EGFR-modulated TME changes in IBC.
3. Develop novel combination immunotherapy by modulating the TME of IBC using EGFR-targeted therapy.

Role: Co-Investigator

Overlap: None

SHETH, Rahul

CURRENT

n/a (Sheth)
Title: *Developing Gellan Gum and PLGA Variants for Delivery of Immunotherapeutics to Solid Tumors*

Time Commitments: 0.12 calendar months (1% effort)

Supporting Agency: Biocompatibles, Inc.

Grants Officer: Duncan Kennedy, Duncan.kennedy@btgplc.com, and Emily Barnhill, ehbarnhill@mdanderson.org

Performance Period: 03/02/2021-02/07/2024

Level of Funding:

Goal(s): The proposed studies will establish an intratumoral drug delivery system utilizing a delivery medium to elicit an adaptive immune response.

Specific Aims: 1. Define the changes in local and systemic anti-tumor adaptive immunity following percutaneous intratumoral delivery of a hydrogel-immunotherapy platform.
2. Define the changes in local and systemic anti-tumor adaptive immunity following trans-arterial delivery of a microsphere-immunotherapy platform.

Overlap: None

2019-1234 (Sheth)
Title: *Cryoablation Combined with Stereotactic Body Radiation Therapy for the Treatment of Painful Bone Metastases*
Time Commitments: 1.20 calendar months (10% effort)
Supporting Agency: Biocompatibles, Inc.
Grants Officer: Duncan Kennedy, Duncan.kennedy@btgplc.com, and Emily Barnhill, ehbarnhill@mdanderson.org
Performance Period: 10/13/2020-02/07/2024
Level of Funding:
Goal(s): This study will evaluate the cryoablation therapy in combination with radiation therapy used in patients for the palliation of painful bone metastases.
Specific Aims: 1. To determine the efficacy of cryoablation in combination with stereotactic body radiation therapy (SBRT) or SBRT only for the treatment of painful bone metastases.
2. To assess technical success for cryoablation.
3. To investigate the local microenvironmental changes following SBRT and cryoablation combined with SBRT to bone metastases.
Overlap: None

R44 CA273961 (Iftimia)
Title: *Intelligent Optical Probe for Guiding Core Needle Biopsy Procedures*
Time Commitments: 0.36 calendar months (3% effort)
Supporting Agency: NIH/NCI
Grants Officer: Cornice Young, youngce2@mail.nih.gov
Performance Period: 04/01/2022-03/31/2024
Level of Funding:
Goal(s): Successful completion of this program will lead to the development of a novel tool for guiding core needle biopsy procedures.
Specific Aims: 1. Revise instrumentation and probe design to meet clinical requirements for ease of use, safety, and reliable feedback.
2. Evaluate optical biopsy guidance probe safety, ease of use, and capability to produce high quality images of the human solid tumors that can be used to reliably determine tissue cellularity.
3. Assess optical imaging findings against pathology results and train software algorithm to automatically interpret these images.
Role: Subcontract PI
Overlap: None

N/A (Sheth)
Title: *Collaborative Research: CPS: Medium: A CPS Approach To Tumor Immunomodulation; Sensing, Analysis, And Control to Prime Tumors to Immunotherapy*
Effort: 0.60 calendar months (5% effort)
Supporting Agency: National Science Foundation (NSF)/Kansas State University
Grants Officer: Irene C. Sattler, isattler@nsf.gov
Performance Period: 07/15/2021-06/30/2024
Level of Funding:

Goal(s): The CPS program aims to develop the core research needed to engineer these complex CPS, some of which may also require dependable, high confidence, or provable behaviors.

Specific Aims: 1. In vivo measurements and immune profiling will be conducted in male and female mice (n=20), randomly allocated in a 1 :1 ratio to experimental groups at age 2 months.
2. In this experiment, we will determine the influence of therapies targeting tumor microenvironmental biophysical properties both discretely and in concert with immunotherapies.

Overlap: None

(THIS AWARD)

W81XWH-20-10257

(Aparicio)
Title: PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)

Time Commitments: 0.60 calendar months (5% effort)

Supporting Agency: DOD

Grants Officer: Kenneth E. Grenier, kenneth.e.grenier2.civ@mail.mil

Performance Period: 09/01/2020-08/31/2024

Level of Funding: The overall goal of this study is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.

Goal(s): 1. Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC.
2. Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.

Specific Aims: Co-Investigator

Role: None

Overlap:

n/a

(Pant)
Title: 2016 Pancreatic Cancer Action Network-Precision Promise Clinical Trial Consortium Sites

Time Commitments: 0.12 calendar months (1% effort)

Supporting Agency: Pancreatic Cancer Action Network

Grants Officer: Not available

Performance Period: 05/28/2020-05/27/2025

Level of Funding:

Goal(s): Precision Promise is a multi-center, seamless Phase 2/3 platform trial designed to evaluate multiple regimens in metastatic pancreatic cancer.

Specific Aims: 1. To determine short and long-term safety signals of the pamrevlumab arm in pancreatic cancer patients vs. SOC.
2. To determine progression-free survival (PFS) for the pamrevlumab arm vs. SOC.
3. To measure rates of overall response (CR and PR) by RECIST 1.1 criteria, and duration of response, for the pamrevlumab arm vs. SOC.
4. To assess longitudinally quality of life (QOL) for patients treated on the pamrevlumab arm vs. SOC.

Overlap: None

(NEW)

Title: A Phase I Study of Reirradiation with NBTXR3 for Inoperable Locoregional Recurrent Non-Small Cell Lung Cancer (NSCLC)

Time Commitments: 0.12 calendar months (1% effort)

Supporting Agency: Nanobiotix, S.A.

Grants Officer: Morgane Huguet, 60 Rue de Wattignies, 75012 Paris, France

Performance Period: 06/30/2020-06/29/2025

Level of Funding: To determine the recommended phase II dose (RP2D) of NBTXR3

Goal(s): activated by radiotherapy in patients with inoperable, locoregional recurrent NSCLC, previously treated with definitive radiation therapy.

Aims:

1. To evaluate the safety and feasibility of reirradiation with NBTXR3 in patients with inoperable, locoregionally recurrent NSCLC.
2. To evaluate the anti-tumor response of reirradiation with NBTXR3 in patients with inoperable, locoregionally recurrent NSCLC.
3. To evaluate time-to-event outcomes after reirradiation with NBTXR3 in patients with inoperable, locoregionally recurrent NSCLC.

Overlap: None

Title: A Phase 1b/2 Pressure Enabled Regional Immuno-Oncology Study of Hepatic Arterial Infusion of SD-101 with Systemic Checkpoint Blockade for Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

Time Commitments: 0.24 calendar months (2% effort)

Supporting Agency: TriSalus Life Sciences

Grants Officer: Not available

Performance Period: 01/20/2022-01/19/2026

Level of Funding:

Goal(s): Phase 1b – To determine the safety of and to identify the maximum tolerated dose (MTD) or optimal dose of PEDD/HAI of SD-101 alone, the MTD or optimal dose of SD- 101 in combination with pembrolizumab or both nivolumab and ipilimumab in patient with HCC or ICC.

Phase 2 –To assess the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 ORRto PEDD/HAI of SD-101 in combination with intravenous (IV) immune checkpoint blockade. The checkpoint regimen used in combination with SD-101 will be chosen based on safety and response data from Phase 1b.

Specific Aims:

1. Phase 1b – To assess preliminary efficacy in terms of RECIST for immune based therapeutics (iRECIST) ORR, modified RECIST (mRECIST) ORR, RECIST 1.1 hepatic-specific response rate (HRR), overall PFS, and clinical benefit (CR + partial response [PR] + stable disease [SD]).

2. Phase 2 – To assess the duration of response (DOR), 12-month OS, and safety/toxicity of the chosen MTD or optimal dose of SD-101 in combination with CPI.

Overlap: None

(NEW)

Title: *Phase II Study of NBTXR3 Activated by Radiation and Combined with Pembrolizumab for Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma with Limited PD-L1 Expression or Refractory to PD-1 Blockade*

Time Commitments: 0.12 calendar months (1% effort)

Supporting Agency: Nanobiotix S.A.

Grants Officer: Morgane Huguet, 60 Rue de Wattignies, 75012 Paris, France

Performance Period: 10/01/2020-03/31/2026

Level of Funding:

Goal(s): To evaluate tumor response of NBTXR3 activated by RT in combination with pembrolizumab in patients with R/M HNSCC.

Specific Aims:

1. To evaluate tumor response of NBTXR3 activated by SBRT reirradiation with concurrent pembrolizumab and dose reduction IMRT or IMPT reirradiation with concurrent pembrolizumab.
2. To assess the safety profile of NBTXR3 activated by RT in combination with pembrolizumab in patients with R/M HNSCC.
3. To evaluate time-to-event outcomes of NBTXR3 activated by RT in combination with pembrolizumab in patients with R/M HNSCC.

Overlap: None

(NEW)

R37 CA269622

Title: *(Sheth)
An Image-Guided Immunotherapy and Hyperthermia Delivery Device to Overcome Barriers to Tumor Immunity for Advanced Hepatocellular Carcinoma*

Time Commitments: 1.80 calendar months (15% effort)

Supporting Agency: NIH/NCI

Grants Officer: Joy Kearse, kearsej@mail.nih.gov

Performance Period: 03/01/2023-02/29/2028

Level of Funding:

Goal(s): Long-term goal is to develop image-guided interventions that expand the clinical impact of immunotherapies for patients with advanced HCC.

Specific Aims:

1. Define the influence of injection technique and hyperthermia on i.t. delivery.
2. Determine the tumor microenvironmental ramifications of hyperthermia as a function of thermal dose and time.
3. Characterize the local and abscopal effects of hyperthermia when combined with i.t. immunotherapy.

Overlap: None

Title: *A Phase 1/1b Pressure Enabled Regional Immuno-Oncology Study of Pancreatic Retrograde Venous Infusion of SD-101 Alone and with Checkpoint Blockade for Locally Advanced Pancreatic Ductal Adenocarcinoma*

Time Commitments: 0.36 calendar months (3% effort)

Supporting Agency: TriSalus Life Sciences

Grants Officer: Not available

Performance Period: 06/17/2022-03/01/2028

Level of Funding:	
Goal(s):	To determine the maximum tolerated dose or optimal dose of SD-101 alone administered via PRV1. Phase 1b – To determine the safety of SD-101 administered via PRV1 in combination with pembrolizumab and to assess the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 overall response rate.
Specific Aims:	1. Phase 1 – To assess the RECIST v1.1 ORR. 2. Phase 1b - To assess progression-free survival (PFS) and the 12-month overall survival (OS) to PRV1 of SD-101 in combination with intravenous (IV) immunological checkpoint blockade. 3. Phase 1b – To assess preliminary efficacy in terms of RECIST for immune based therapeutics (iRECIST) ORR, RECIST 1.1 pancreatic-specific response rate (PRR), duration of response (DOR), and clinical benefit (complete response [CR] + partial response [PR] + stable disease [SD]).
Overlap:	None
NCT04683939	(Pant)
Title:	<i>2021-0481: Phase I/IIa, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT141 as a monotherapy and in combination with other anti-cancer agents in patients with CLDN18.2-positive solid tumors</i>
Time Commitment:	0.12 calendar months (1% effort)
Supporting Agency:	BioNTech Diagnostics
Grants Officer:	Not available
Performance Period:	08/26/2021-08/25/2028
Level of Funding:	
Goal(s):	To assess the safety and tolerability of BNT141 at different dose levels. To characterize the PK profile of the BNT141-encoded protein RiboMab01.
Specific Aims:	1. To characterize the PK profile of the BNT141-encoded protein RiboMab01. 2. To evaluate the anti-tumor activity of BNT141 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. 3. To evaluate the immunogenicity of BNT141.
Overlap:	None
(NEW)	
NCT05497778	(Pant)
Title:	<i>2022-0130: A Phase 1b Study of Gemcitabine and Nab- Paclitaxel in Combination with IM156 in Patients with Advanced Pancreatic Cancer</i>
Time Commitment:	0.24 calendar months (2% effort)
Supporting Agency:	ImmunoMet
Grants Officer:	Not available
Performance Period:	08/08/2022-08/07/2029
Level of Funding:	
Goal(s):	We hypothesize that the combination of Gem, NP and IM156 will provide a safe and effective first line treatment strategy for patients with metastatic PDAC.

Specific Aims: 1. To evaluate the safety and tolerability of IM156 with Gem+NP in patients with metastatic PDAC.
2. To evaluate the efficacy of IM156 with Gem+NP in patients with metastatic PDAC

Overlap: None

PREVIOUS (Recently completed since the last report)

N/A

SUBUDHI, Sumit

CURRENT

NCT03431350

(Subudhi)

Title:

2017-0952: A Phase 1b-2 Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer

Time Commitments:

0 calendar months

Supporting Agency:

Janssen Research and Development LLC

Grants Officer:

Kerri Anne Sitze, KSitze@ITS.JNJ.com

Performance Period:

02/27/2018-04/14/2024

Level of Funding:

Goal(s):

The purpose of this study is to: a) establish the recommended phase 2 dose (RP2D) and to evaluate the antitumor activity and safety of niraparib combination therapies (Combinations 1 and 2) and b) to determine the relative bioavailability of niraparib and abiraterone acetate (AA) in combination (Combination 3) in participants with metastatic castration-resistant prostate cancer (mCRPC).

Specific Aims:

Not applicable

Overlap:

None

(THIS AWARD)

W81XWH-20-1-0257

(Aparicio)

Title:

PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)

Time Commitments:

1 calendar months (1% effort)

Supporting Agency:

Department of Defense

Grants Officer:

Kenneth E. Grenier, kenneth.e.grenier2.civ@mail.mil

Performance Period:

09/01/2020-08/31/2024

Level of Funding:

Goal(s):

Our overall goal is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.

Specific Aims:

1. Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC.
2. Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.

Role:

Co-Investigator

NCT03835533

(Subudhi)

Title: 2019-0140: A Multicenter, Open-Label, Exploratory Platform Study to Evaluate Biomarkers and Immunotherapy Combinations for the Treatment of Patients with Metastatic Castration Resistant Prostate Cancer

Time Commitments: 0 calendar months

Supporting Agency: Parker Institute for Cancer

Grants Officer: Ari Bitton, abitton@parkerici.org

Performance Period: 11/14/2019-11/13/2026

Level of Funding:

Goal(s): This study is designed to evaluate multiple clinical hypotheses and mechanistically-defined combinations to evaluate the safety and efficacy of immunotherapy combinations in participants with mCRPC who have received prior secondary androgen receptor signaling inhibitor therapy (e.g., abiraterone, enzalutamide, apalutamide).

Specific Aims: Not applicable.

Overlap: None

NCT04100018 (Subudhi)

Title: 2020-0072: Advance Funding-Rapid Activation Program-2020-0072-A Phase 3 Randomized, Double-Blind Study of Nivolumab or Placebo in Combination with Docetaxel, in Men with Metastatic Castration-resistant Prostate Cancer, protocol number CA209-7DX

Time Commitments: 0 calendar months

Supporting Agency: Bristol-Myers Squibb

Grants Officer: Michelle Kirchoff, michelle.kirchoff@syneoshealth.com

Performance Period: 05/04/2020-05/03/2027

Level of Funding:

Goal(s): The purpose of this study is to test the safety and effectiveness of nivolumab with docetaxel in men with advanced castration resistant prostate cancer who have progressed after second-generation hormonal manipulation.

Specific Aims: Not applicable

Overlap: None

NCT04381832 (Subudhi)

Title: 2020-0376: A Phase 1b/2, Open-Label, Randomized Platform Study Evaluating the Efficacy and Safety of AB928-Based Treatment Combinations in Patients with Metastatic Prostate Cancer

Effort: 0 calendar months

Supporting Agency: Arcus Biosciences

Grants Officer: Amy Ford, Amy.Ford@iqvia.com

Performance Period: 06/24/2020-06/23/2027

Level of Funding:

Goal(s): This is a Phase 1b/2, open-label, multicenter platform trial to evaluate the antitumor activity and safety of etrumadenant (AB928)-based combination therapy in participants with metastatic castrate resistant prostate cancer (mCRPC).

Specific Aims: Not applicable.

Overlap: None

NCT04631601 (Subudhi)
Title: 2020-0568: A Master Protocol Evaluating the Safety and Efficacy of Therapies for Metastatic Castration-resistant Prostate Cancer (mCRPC)
Time Commitments: 0 calendar months
Supporting Agency: Amgen Inc.
Grants Officer: Amanda Pratt, amandap@amgen.com
Performance Period: 11/04/2020-11/03/2027
Level of Funding:
Goal(s): This is a master protocol designed to evaluate the safety and efficacy of investigational therapies in participants with metastatic castration-resistant prostate cancer (mCRPC).
Specific Aims: Not applicable
Overlap: None

PREVIOUS (Recently completed since the last report)

D2018-014 (Subudhi)
Title: Targeting the Immunosuppressive Compartment of the Prostate Cancer Bone Metastatic Microenvironment to Improve Clinical Outcomes
Time Commitments: 9.0 calendar months (75% effort)
Supporting Agency: V Foundation/Lloyd Fam Clin Oncol Scholar Award
Grants Officer: Sommer Axner, saxner@v.org
Performance Period: 02/01/2018-02/01/2023 NCE
Level of Funding:
Project Goals: To improve clinical outcomes in patients with advanced prostate cancer through rationally designed immune checkpoint therapy-based combinatorial strategies that target the immunosuppressive tumor microenvironment.
Specific Aims: 1. Improve clinical outcomes by overcoming adaptive resistance within the tumor microenvironment.
2. Improve effector immune responses within the tumor micro-environment.
3. Conduct co-clinical trials in murine models to identify novel T cell and macrophage targets.
Overlap: None

Prostate Moon Shot (Logothetis, Aparicio, and Navin)
Title: Priority Project 2: Targeting Prostate Tumor-Induced Bone Formation to Reserve the Immunosuppressive Bone-TME And Improve the Efficacy of Immune Checkpoint Therapies
Time Commitments: 0 calendar months
Supporting Agency: MD Anderson Moon Shot Program
Grants Officer: Carrie C. Feighl, research_finance@mdandeson.org
Performance Period: 09/01/2022-08/31/2023
Level of Funding:
Goal(s): The overall goal of this project is to determine whether inhibiting recruitment and activation of myeloid suppressor cells into the bone tumor microenvironment represents a therapeutic strategy to improve efficacy of immune checkpoint therapies in metastatic castrate-resistant prostate cancer.

Specific Aims: Not applicable.
Role: Co-Leader
Overlap: None

Prostate Moon Shot (Logothesis, Aparicio, and Navin)
Title: *Priority Project 3: Development of Bispecific Immunotherapy Strategies to Overcome the Immunosuppressive Prostate Tumor Microenvironment*

Time Commitments: 0 calendar months
Supporting Agency: MD Anderson Moon Shot Program
Grants Officer: Carrie C. Feighl, research_finance@mdanderson.org
Performance Period: 09/01/2022-08/31/2023
Level of Funding:
Goal(s):

The goal of this project is to build on our experience with immune checkpoint therapies (ICTs) to improve outcomes by developing bispecific immunotherapy strategies to overcome T cell exclusion within the immunosuppressive prostate tumor microenvironment.

Specific Aims: Not applicable.
Role: Clinical Co-Leader
Overlap: None

P50 CA140388-10 (Logothesis/Thompson)
Title: *MD Anderson Cancer Center Prostate Cancer SPORE*
Project 1: Integrating Ipilimumab Immunotherapy with Approved Treatment Strategies in CRPC

Time Commitments: 0.36 calendar months (3% effort)
Supporting Agency: NIH/NCI
Grants Officer: Ashley Salo, ashley.salo@nih.gov
Performance Period: 09/01/2016-08/31/2023 NCE
Level of Funding:

Goal(s): To rationally integrate anti-CTLA-4 (ipilimumab) immunotherapy with agents targeting the AR signaling pathway to provide durable clinical benefit with improved survival in patients with prostate cancer and utilize novel imaging techniques to accurately identify tumor responses.

Specific Aims: 1. Identify biological changes indicative of mechanistic pathways that contribute to clinical outcomes in matched tumor and blood specimens obtained from prostate cancer patients given drugs targeting the AR signaling pathway plus anti-CTLA-4 (ipilimumab) immunotherapy.
2. Determine clinical outcomes after treatment with AR-targeting agents (ARN-509 + abiraterone acetate) followed by concurrent anti-CTLA-4 (ipilimumab) immunotherapy and prospectively evaluate the effectiveness of selected biological pathways identified in Aim 1 to be indicative of mechanistic pathways that contribute to clinical outcomes.
3. Determine the efficacy of targeting B7-H3 and B7-H4 with radiolabeled monoclonal antibodies as a non-invasive means to detect prostate cancer.

Role: Co-Investigator
Overlap: None

ZHANG, Miao**CURRENT***W81XWH-21-1-0522**(Wang)*

Title:

PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer

Time Commitments:

0.36 calendar (3% effort), Year 3 only

Supporting Agency:

DOD-PCRP-Idea

Grants Officer:

Kimberly Carter, Kimberly.m.carter47.civ@mail.mil

Performance Period:

09/01/2021-08/31/2024

Level of Funding:

Goal(s):

Our overall goal is to develop combination therapy to improve the clinical outcome of platinum-taxane chemotherapy in patients with NEPC.

Specific Aims:

1. Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs.
2. Examine the mechanism(s) by which KDM4A regulates UPR signaling.
3. Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.

Role:

Co-Investigator

Overlap:

None

(THIS AWARD)*W81XWH-20-1-0257**(Aparicio)*

Title:

PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)

Time Commitments:

0.12 calendar months (1% effort), Year 1; 0.60 calendar months (5% effort), Year 2; 1.20 calendar months (10% effort), Years 3 and 4

Supporting Agency:

DOD

Grants Officer:

Kenneth E. Grenier, kenneth.e.grenier2.civ@mail.mil

Performance Period:

09/01/2020-08/31/2024

Level of Funding:

total

Goal(s):

The overall goal is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.

Specific Aims:

1. Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC.
2. Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.

Role:

Co-Investigator

*RP220410**(Rai)*

Title:

Mechanisms and Therapies Focused on Epigenomic Alterations in Therapy-Resistant Prostate Cancers

Time Commitment:

0.24 calendar months (2% effort)

Supporting Agency:

CPRIT

Grants Officer:

Patty Moore, pmoore@cprit.texas.gov

Performance Period:

03/01/2022-02/28/2025

Level of Funding:

Goal(s): The overall goals of this proposal are to define functional driver enhancer elements that cause therapy resistance, characterize AR, FOXA1, HOXB13, and SOX4 as core TFs mediating epigenome reprogramming, and examine whether targeting enhancers using MLL/MENIN inhibitors alone or in combination with enzalutamide can be useful in suppressing growth of aggressive therapy-resistant prostate tumors in GEMMs for preclinical assessment.

Specific Aims: 1. Identify functional enhancer elements, their gene targets and downstream mechanism in specific epigenetic subtypes (EPIC).
2. Determine the molecular mechanism of EPIC-specific patterns of aberrant enhancer activation.
3. Determine the efficacy of BRD inhibition alone or in combination with pathway inhibitors for specific CMS subtypes.

Role: Collaborator

Overlap: None

(NEW)

W81XWH-22-1-0188

(Zurita)

Title:

PC210046P1: Revisiting Antiangiogenic Therapy to Target Prostate Cancer Metabolism

Time Commitments:

0.12 calendar months (1% effort)

Supporting Agency:

DOD

Grants Officer:

Joshua McKean; 301-619-4046, joshua.d.mckean3.civ@mail.mil

Performance Period:

09/01/2022-08/31/2025

Level of Funding:

Goal(s):

The goal of this proposal is to evaluate whether co-targeting cancer cell anaplerotic metabolism and angiogenesis can synergize to treat advanced prostate cancer.

Specific Aims:

1. Evaluate angiogenesis as a mechanism of resistance to CAMKK2 inhibition and anaplerotic stress.
2. Determine if a clinical-grade inducer of anaplerotic stress sensitizes advanced prostate cancers to the antitumor effects of antiangiogenic therapy.
3. Assess whether anaplerotic signaling predicts sensitivity to antiangiogenic therapy in patients.

Role:

Collaborator

Overlap:

None

(NEW)

R01 CA275138-01A1

(Frigo/Zurita)

Title:

Revisiting Antiangiogenetic Therapy to Target Prostate Cancer Metabolism

Time Commitments:

0.24 calendar months (2% effort)

Supporting Agency:

NIH/NCI

Grants Officer:

Joy Kearse, 301-631-3002, kearsej@mail.nih.gov

Performance Period:

05/12/2023-04/30/2028

Level of Funding:

Goal(s):

To evaluate whether co-targeting cancer cell anaplerotic metabolism and tumor angiogenesis can synergize to treat hormone-sensitive prostate cancer, and to determine whether biomarkers of anaplerotic signaling can

Specific Aims: predict response to antiangiogenic therapy and therefore, guide patient selection.

1. Evaluate angiogenesis as a mechanism of resistance to CAMKK2 inhibition and anaplerotic stress.
2. Determine if a clinical-grade inducer of anaplerotic stress sensitizes advanced prostate cancers to the antitumor effects of antiangiogenic therapy.
3. Assess whether anaplerotic signaling predicts sensitivity to antiangiogenic therapy in patients.

Role: Co-Investigator

Overlap: None

PREVIOUS

N/A

I, PD/PI and other senior/key personnel confirm that I:

- Certify that the current and pending support provided on the application is current, accurate and complete;
 - Agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award; and
 - Have been made aware of the requirements under Section 223(a)(1) of this Act. DOD General Application Instructions 18
- False, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties (U.S. Code, Title 18, Section 1001)

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations - academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) - that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner's contribution to the project (identify one or more)

- Financial support;
- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner's facilities for project activities);
- Collaboration (e.g., partner's staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
- Other.

Organization Name:	Janssen Pharmaceuticals.
Location of Organization:	Headquarters in Beerse, Belgium.
Partner's contribution to the project:	Provides cetrelimab and niraparib.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org/eBRAP/public/index.htm> for each unique award.*

Nothing to report.

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.*

Not applicable.

- 9. APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. DO NOT RENUMBER PAGES IN THE APPENDICES.*

Not applicable