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CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute, Boston, MA

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14. ABSTRACT

Alterations in DNA damage repair genes are common in metastatic castration-resistant prostate cancer (mCRPC), and are implicated in clinical responses to carboplatin, PARP inhibitors and immunotherapeutics. The ATR kinase is involved in the response to a wide range of DNA damage and replication stress, and ATR inhibitors have been previously demonstrated in model systems to have synergistic activity with platinum compounds, and to have activity in homologous recombination (HR)-deficient cells rendered resistant to PARP inhibitors and cells deficient for ATM expression.
Hypothesis/Objective: We hypothesize that the ATR inhibitor M6620 in combination with carboplatin will demonstrate clinical activity in mCRPC, both in HR-deficient patients (even with PARP inhibitor resistance) and potentially HR-proficient patients due to synergistic activity of M6620 with carboplatin related to induction of replication stress. I am leading NCI protocol # 10191, A Phase 2 study of M6620 with carboplatin compared to docetaxel with carboplatin in mCRPC (n=136 pts). This study mandates pre-treatment tumor biopsy and research blood collections for circulating cell-free DNA (cfDNA) analyses pre-treatment, every 3 cycles on treatment and at end of study. This proposal is for biomarker studies from these biospecimens and for functional studies in model systems to define genetic correlates of response and resistance to therapy.

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INTRODUCTION

Alterations in DNA damage repair (DDR) genes are common in metastatic castration-resistant prostate cancer (mCRPC), and are implicated in responses to carboplatin, PARP inhibitors and immunotherapeutics. Inhibitors of the ATR kinase, which is involved in the DDR response, have been demonstrated to have synergistic activity with platinum compounds in preclinical models. We therefore conducted a Phase 2 study of the ATR inhibitor M6620+carboplatin vs. docetaxel+carboplatin in mCRPC (NCI protocol # 10191, NCT03517969). The trial mandates pre-treatment tumor biopsy and research blood collections for circulating cell-free DNA (cfDNA) analyses pre-treatment, every 3 cycles on treatment and at end of study. This proposal is for biomarker studies from these biospecimens and for functional studies in model systems to define genetic correlates of response and resistance to therapy.

KEYWORDS

Prostate cancer, carboplatin, ATR, VX-970, M6620, berzosertib, castration resistant, DDR, HRR

ACCOMPLISHMENTS:

For NCI protocol # 10191, patients previously treated with at least one secondary hormonal therapy and taxane underwent mandatory pre-treatment biopsy and were randomized 1:1 to receive Arm A (docetaxel 60 mg/m2 day 1 + carboplatin AUC 4 day 1) or Arm B (M6620 90 mg/m2 days 2,9 + carboplatin AUC 5 day 1) every 21 days. Patients randomized to Arm A who were not candidates for docetaxel received carboplatin AUC 5 monotherapy. Stratification factors were 1) prior PARP inhibitor (yes vs. no) and 2) evaluable disease by RECIST 1.1 (yes vs. no). Patients on Arm A crossed over to Arm B (M6620+carboplatin) at the earlier of PSA or radiographic progression. The primary endpoint was overall response rate (ORR; PSA reduction by ≥ 50% or radiographic response by RECIST 1.1). Secondary endpoints included time to PSA progression, radiographic PFS (rPFS), PFS by PCWG3 criteria, and adverse events (AEs) in each arm. Planned enrollment was 136 patients (for 130 to be treated), with interim analysis for futility after 65 patients were treated.

Seventy-three patients were randomized between 6/2019 and 7/2020; 34 patients were treated on Arm A (26 carboplatin+docetaxel; 8 carboplatin alone) and 31 on Arm B. Median number of prior systemic therapies (excluding ADT, 5α-reductase inhibitors, 1st generation antiandrogens) was 4 (range 2-8). Median treatment duration was 3 cycles, and 4 patients in each arm discontinued for AEs. Grade 3 or higher treatment-related AEs (TrAE) were seen in 13(38%) patients in Arm A and 21(68%) in Arm B. Patients in Arm B had greater frequency of grade 3-4 thrombocytopenia (8[26%] vs. 3[9%]). 1 pt in Arm B had grade 5 sepsis attributed to study treatment. ORR was 15% in Arm A (5/34; 5/26[19%] in patients who received carboplatin+docetaxel) and 0% in Arm B (0/31). 14 patients in Arm A crossed over, with no subsequent responses seen. Median rPFS was 2.1(95% CI:2.0,3.2) mo in Arm A and 2.4(1.9,4.2) mo in Arm B. At planned interim analysis, trial enrollment and crossover to Arm B were halted due to futility.

At the time of this writing, biospecimens from trial participants have been shipped to the laboratories performing the relevant analyses as detailed below.

o What were the major goals of the project? / What was accomplished under these goals?

Specific Aim 1: To correlate genetic and molecular features from pre-treatment tumor biopsy and cfDNA with clinical outcomes for M6620+carboplatin and docetaxel+carboplatin

Major Task 1: IRB and HRPO approval

The biomarker analyses from tumor and blood specimens from participants in the clinical trial are included in the study protocol and were approved by the Central IRB (CIRB). In addition, a secondary use protocol that includes only those activities funded by the DoD (as referenced in the approved Statement of Work) was written and has been approved by the Dana-Farber/Harvard Cancer Center (under DF/HCC protocol # 20-661) and by HRPO. Letters documenting continuing CIRB approval for protocol # 10191, IRB approval for DF/HCC protocol # 20-661 and HRPO approval are attached.

Major Task 2: Whole exome sequencing analysis of pre-treatment tumor biopsy specimens

While pre-treatment biopsy was mandatory for trial participation, this requirement was waived during the COVID-19 pandemic during a time when research biopsies were not being performed at many institutions. Of the 73 randomized patients, 68 patients had pre-treatment biopsies performed and sent to the NCI Biorepository for analysis.

Biomarker conference call with NCI/CTEP (Charles Kunos, Jeff Moscow, Tracy Lively, Melissa-McKay-Daily, Chaz Stephens) on January 26, 2021 confirmed plan to complete the biomarker studies detailed in the protocol including whole exome sequencing to assess genetic features correlating with response to carboplatin + docetaxel and to clinical benefit in both arms of the study.

In the past year, Svetlana Nazarenko in the CTEP Regulatory Affairs Branch (RAB) prepared and routed the biospecimen transfer agreement for transfer of these specimens to the NCI Molecular Characterization (MoCHa) laboratory for whole exome sequencing. DNA and RNA were successfully extracted from the pre-treatment specimens, though three of these cases initially had low yield so required coring and re-extraction. After undergoing additional quality check steps, 39 of the 65 treated patients had extracted DNA felt adequate for whole exome sequencing (WES). These were shipped on 3/14/22 from the NCI Biorepository and received at the MoCha laboratory on 3/15/22.

Major Task 3: Circulating cell-free DNA analysis from pre-treatment specimens

We have nearly completed pilot projects for analysis of circulating cell-free DNA specimens from banked plasma specimens from patients treated with standard of care Radium-223 and docetaxel using the targeted sequencing panel detailed in the grant application developed in collaboration with Dr. Franklin Huang currently at University of California San Francisco. This panel includes exonic regions of 320 genes (including DNA damage repair genes, genes previously reported to be significantly mutated in prostate cancer, genes with mutations detected in African American patients), the AR enhancer, and intronic regions of ETV1, BRAF, SLC45A3, ETV4, ETV5, ERG, TMPRSS2, FOXA1, RAF1.

We have established a workflow for circulating cell-free DNA sequencing, which starts with ultra-low pass whole genome sequencing (ULP-WGS) library construction using a 6 base pair Unique Molecular Identifier (UMI). UMIs aid in identification of PCR duplicates to distinguish true mutations from PCR errors/sequencing errors based on consensus among reads sharing same the index. Sequencing data from ULP-WGS is used to derive tumor fraction using a previously reported computational tool called ichorCNA. The same library from ULP-WGS is selected in hybrid capture using custom targeted panel with a goal 10,000x – 25,000x mean target coverage (MTC) depending on tumor fraction, with 10,000x MTC for specimens with tumor fraction > 10% and 25,000x for < 10%.

Preliminary metrics from sequencing suggest excellent target recovery of > 90%. However, recovery of DNA duplexes is limited at this Mean Target Coverage per Figure 1.

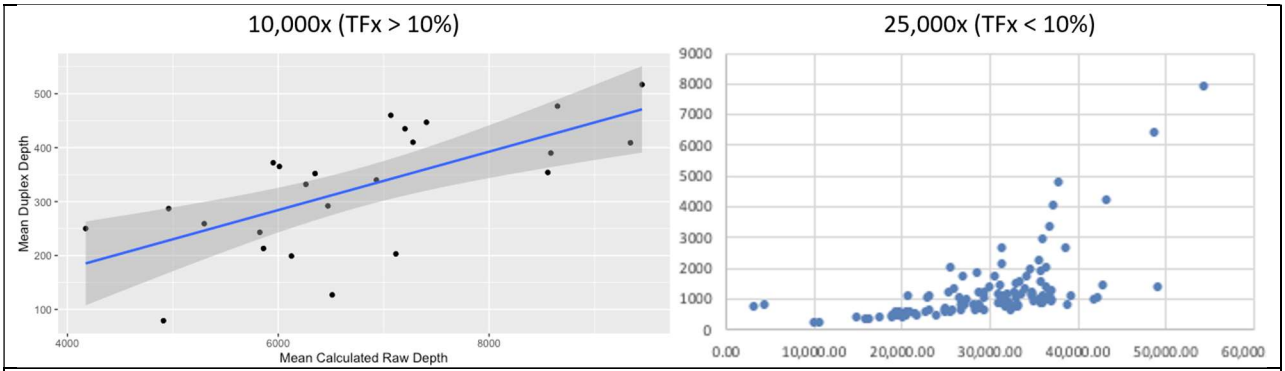


Figure 1. Mean calculated raw depth (x-axis) and mean duplex depth (y-axis) in deep targeted sequencing from banked plasma specimens from prostate cancer patients treated with standard of care Radium-223 at 10,000x mean target coverage for specimens with tumor fraction > 10% (left) and at 25,000x mean target coverage for specimens with tumor fraction < 10% (right).

All cfDNA specimens sequenced at 10,000x MTC and most cfDNA specimens sequencing at 25,000x MTC demonstrate mean duplex depth < 1000x, which is suboptimal for high confidence calling of genetic events present at low abundance in the circulation based on duplex consensus. Despite limited recovery of DNA duplexes, targeted panel sequencing from 81 patients treated with docetaxel identified evidence of ETS fusions in 56% (n=45) of samples as well as mutations in genes known to be recurrently mutated in prostate cancer, including TP53 (44%, n=34), AR (14%, n=11), BRCA2 (6%, n=5, with 4 patients having pathogenic germline variants), and CHEK2 (4%, n=3). ichorCNA additionally identified recurrent amplifications in AR (26%, n=21). These findings will be presented at the 2022 ASTRO conference.

Regarding NCI protocol # 10191, NCI biorepository successfully isolated circulating cell-free DNA from plasma for 63 of the 65 treated patients, 93 specimens in total. These 93 specimens were shipped to the Broad Institute 9/28/21 and received 9/29/21. These specimens have undergone ultra-low pass whole genome sequencing, and tumor fraction was estimated using ichorCNA as depicted in Figure 2.

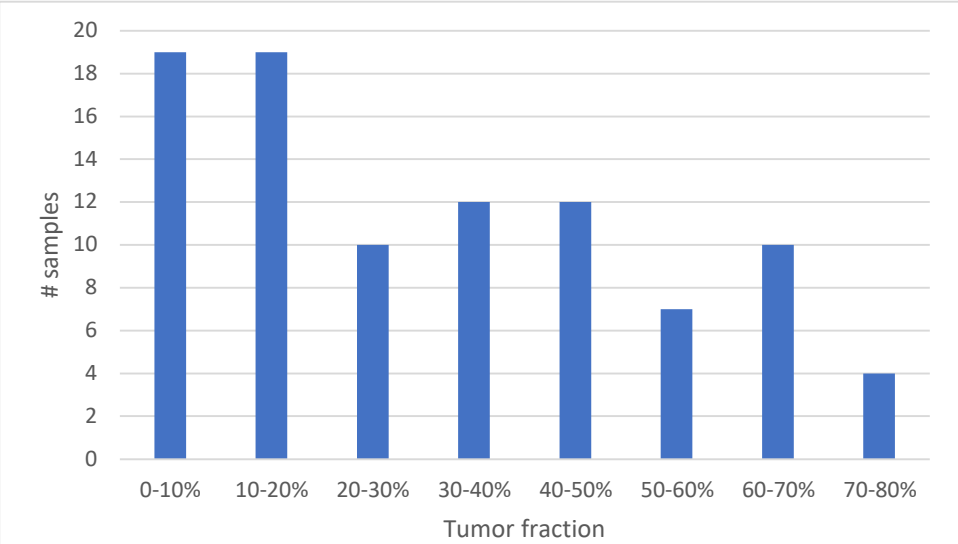
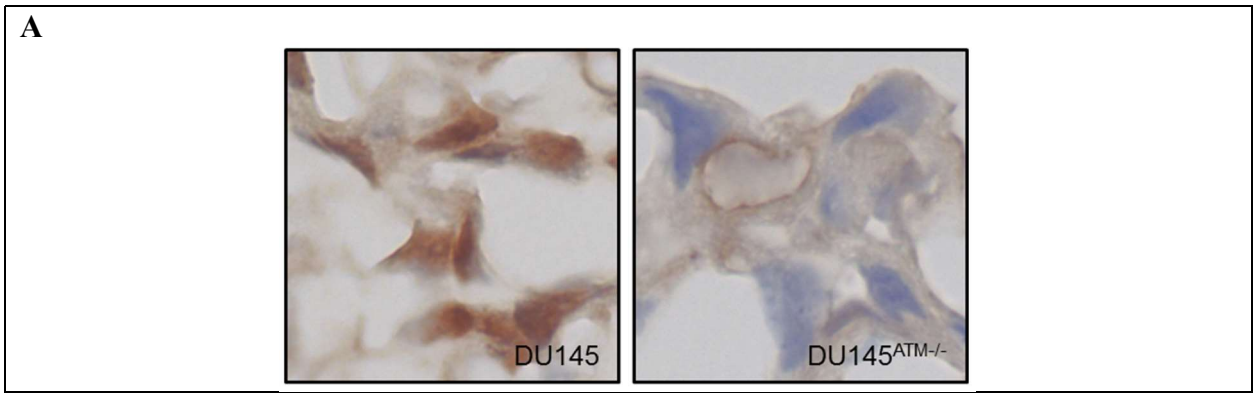


Figure 2. Tumor fraction estimates from 93 cfDNA specimens collected on trial 10191.

Given limited recovery of duplex complexes in our pilot studies, all cfDNA specimens planned to be sequenced for this project will be sequenced at > 50,000x no matter the calculated tumor fraction. Once cfDNA sequencing from these biospecimens is completed, genetic features will be correlated with response to clinical outcomes as for whole exome sequencing as described in Major Task 2

Major Task 4: RAD51 focus formation and ATM IHC assays

The RAD51 focus formation assay was described in the initial grant application and has been validated in prostate cancer model systems.



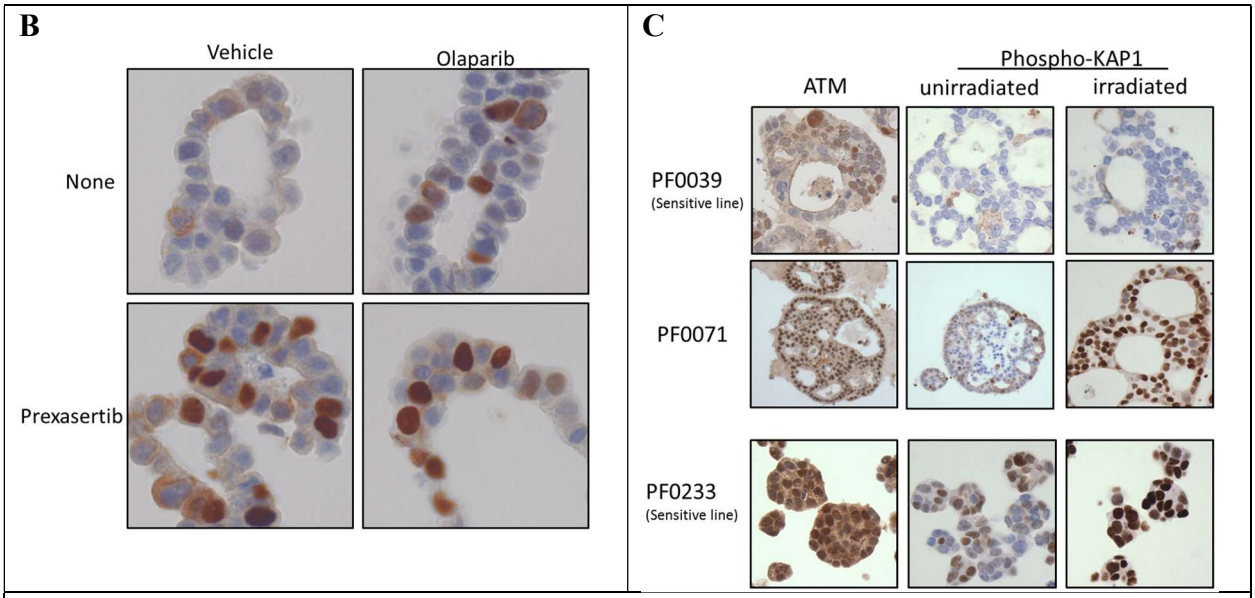


Figure 3. A. ATM staining in ATM wild-type (left) and ATM CRISPR k/o (right) DU145 cells. **B.** Phospho-KAP1 staining in DF59 high grade serous ovarian cancer PDX model with Olaparib, prexasertib or the combination. **C.** Phospho-KAP1 staining in PDX models. PF0039 is ATM-deficient and sensitive to ATR inhibition; KAP1 staining is not increased with irradiation (due to absence of ATM kinase). PF0233 is ATM wild-type with high basal levels of phospho-KAP1 and is sensitive to ATR inhibition; PF0071 is ATM wild-type but with low basal level of phospho-KAP1 and is resistant to ATR inhibition.

We have also optimized the ATM immunohistochemistry assay with the Abcam (Y170) Ab32420 antibody using immortalized fibroblasts from an ataxia telangiectasia patient complemented with exogenously expressed ATM. ATM staining in ATM wild-type (left) and ATM-/- (CRISPR knockout) DU145 cells is shown in Figure 3A. ATM staining is analyzed as follows: 1) ATM is a nuclear protein and expression of ATM is not known to be regulated by the cell cycle 2) ATM scoring: If > 50% of tumor cells stain positive for ATM, the sample is ATM positive, else, the sample is ATM negative 3) Infiltrating lymphocytes and tumor associated stroma are usually ATM positive and can be used as an in-situ reference for staining performance and scoring e.g. variation in tissue processing and its effect on staining.

Since submission of the initial grant application to the DoD, we have added staining for phospho-KAP1 as one of the correlative studies on this protocol. KAP1 (KRAB [Kruppel-Associated Box Domain]-Associated Protein 1) is a protein that in humans is encoded by the TRIM28 gene. KAP1 is phosphorylated by ATM in response to DNA damage, and IHC for phosphorylated KAP1 was optimized using rabbit monoclonal from Cell Signaling clone C42G12. We have demonstrated that phosphorylation of KAP1 increases in response to the PARP inhibitor olaparib, the CHK1 inhibitor prexasertib, and the combination in the DF59 high grade serous ovarian cancer PDX model (Figure 3B). Unpublished data from the laboratory of Dr. Alan D'Andrea suggests that high basal levels of p-KAP1 (which is an indicator of DNA replication stress) in unirradiated tissue may also predict for sensitivity to an ATR inhibitor (Figure 3C).

Since last submission, tumor specimens were cut for immunohistochemistry at the NCI Biorepository and underwent extensive quality control. Of the 65 treated patients, 41 had tissue with adequate tumor content for IHC – these specimens were received at the Center for DNA

Damage and Repair Laboratory at Dana-Farber Cancer Institute on 1/25/22. Staining for RAD51, Geminin, ATM and pKAP1 has been completed and data analysis is in progress.

Specific Aim 2: To discover genetic correlates of resistance to therapy from end-of-study cfDNA and optional biopsies

Major Task 5: Comparison of paired tumor biopsy specimens

Only one study participant underwent optional post-treatment biopsy in the context of ongoing COVID-19 pandemic, so only this paired specimen will be analyzed. If new genetic features are discovered in the post-treatment specimen compared to the pre-treatment, then these would be nominated as potential mediators of resistance for functional analysis.

Major Task 6: Comparison of paired cfDNA specimens

Plasma was isolated for circulating cell-free DNA analysis from trial participants every third cycle of treatment (Arm B: C1D1, C4D1, C7D1, etc.; Arm A: C1D1, C4D1, etc. then C1D1[crossover], C4D1[crossover], etc.). The pre-treatment specimen will be analyzed per Major Task 3 above. The end of treatment specimen will be analyzed pairwise with the pre-treatment specimen - if new genetic features are discovered in the post-treatment specimen compared to the pre-treatment, then these would be nominated as potential mediators of resistance for functional analysis.

Specific Aim 3: To functionally characterize novel genetic alterations identified in pre- and post-treatment specimens

Major Task 7: Characterization of Variants of Uncertain Significance (VUS) in DDR genes

The Mouw laboratory has not begun to generate or characterize DNA repair gene VUSs (Major Task #7) because sequencing information from clinical trial specimens is not yet available due to COVID-related delays over the past year. Once sequencing data from clinical trial specimens becomes available, they will analyze alterations in DNA repair genes and will prioritize recurrent and/or biologically compelling VUSs for study using the techniques outlined in Major Task #7.

Major Task 8: Characterization of drug sensitivity mediated by loss of DNA damage repair genes

Subtask 1: Generate ATM, BRCA1, BRCA2, CHEK2, PALB2, CDK12, FANCA, ERCC6, and RAD51C knockout lines

Subtask 2: Compare properties of the deficient cell lines to their parental (DNA repair proficient) cell lines

We have made significant progress towards the objectives of Major Task #8 (Characterization of drug sensitivity mediated by loss of DNA damage repair genes). We have created several DNA repair deficient isogenic cell pairs (Subtask 1) and are interrogating the impact of DNA repair gene loss (Subtask #2).

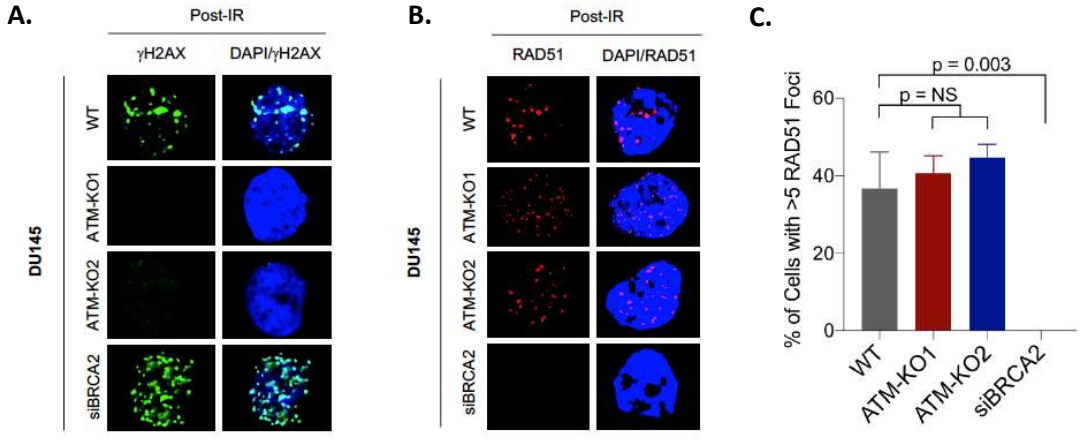


Figure 4: Impact of ATM loss on DNA damage signaling and homologous recombination (HR) function. **A.** ATM loss significantly decreases radiation-induced phospho-H2AX foci formation compared to the wild-type ATM parental cell line or a BRCA2-depleted cell line. **B.** ATM loss does not impact radiation-induced Rad51 foci formation whereas BRCA2 depletion significantly impairs Rad51 foci formation. **C.** ATM deletion does not significantly impair HR function in the DR-GFP reporter assay whereas BRCA2 depletion significantly impairs HR function.

The DNA repair gene for which we have created the most models and collected the most data is ATM. ATM is the second most commonly mutated DNA repair gene in prostate cancer (after BRCA2) and has been associated with aggressive biological and clinical features. We have deleted ATM from 3 different prostate cancer cell lines and have measured the impact of ATM loss on DNA repair capacity and sensitivity to established and emerging prostate cancer therapies. ATM loss significantly abrogates DNA damage signaling as measured by decreased formation of radiation-induced phospho-H2AX foci (Figure 4A). However, ATM loss did not directly impair homologous recombination repair activity, as evidenced by no difference in formation of radiation-induced Rad51 foci in ATM WT vs deleted cell lines (Figure 4B) and no difference in HR efficiency in the DR-GFP reporter assay (Figure 4C). Finally, we observed that ATM loss increased sensitivity to ionizing radiation but had little impact on sensitivity to PARP inhibition across prostate cancer cell line models (Figure 5A, B). Interestingly, ATM loss conferred significantly increased sensitivity to ATR inhibition (Figure 5C), supporting a possible role for ATR inhibitors in the treatment of ATM-mutant prostate tumors.

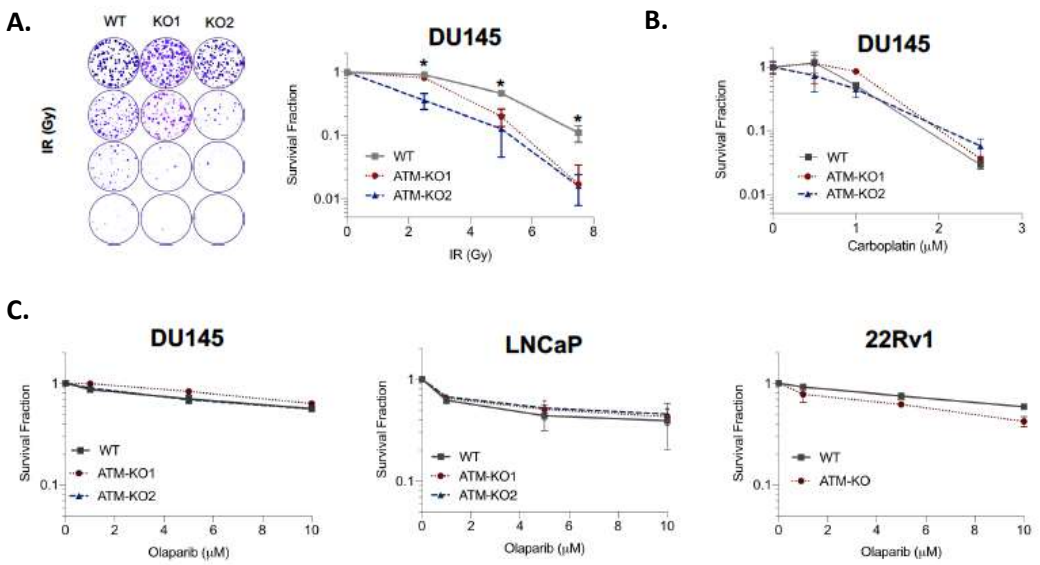


Figure 5: ATM loss and therapeutic sensitivity. **A.** ATM loss increases sensitivity to ionizing radiation (IR). **B.** ATM loss does not increase sensitivity to carboplatin. **C.** ATM loss does not increase sensitivity to the PARP inhibitor olaparib across prostate cancer cell line models.

In addition to ATM, we have also begun to study other DNA repair genes such as PALB2 and BARD1. PALB2 is a binding partner of BRCA2 and PALB2 loss has been associated with homologous recombination deficiency and PARP inhibitor sensitivity in breast and ovarian cancer. BARD1 is a BRCA1 binding partner and BARD1 loss or mutation has also been implicated as a homologous recombination gene of potential clinical relevance in breast and ovarian cancer. To model PALB2 and BARD1 loss, we have to date focused on using siRNAs to transiently deplete either PALB2 or BARD1 from prostate cancer cell lines. These data show that PALB2 or BARD1 loss leads to loss of HR function as measured by loss of radiation-induced Rad51 foci (Figure 6A), the DR-GFP reporter assay (Figure 6B) and also significantly increases in vitro sensitivity to PARP inhibition, with a magnitude of effect similar to BRCA2 loss (Figure 7).

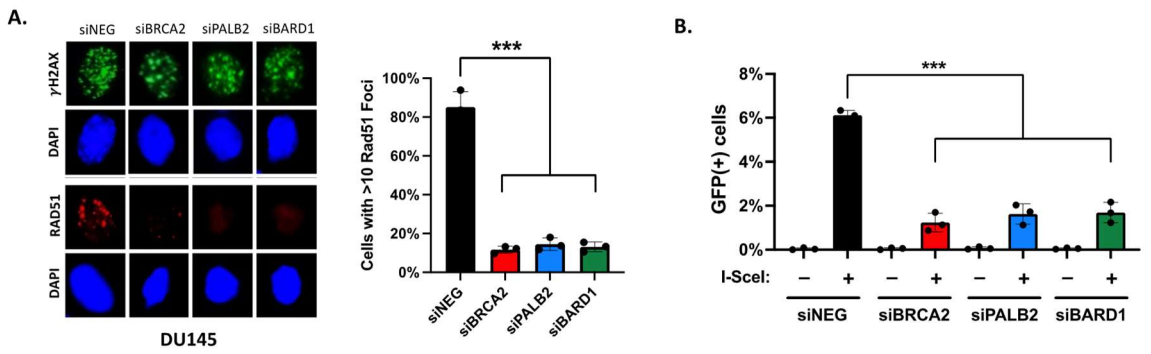


Figure 6: Loss of PALB2 or BARD1 confers homologous recombination (HR) deficiency. A. Loss of PALB2 or BARD1 results in loss of radiation-induced Rad51 foci. B. Loss of PALB2 or BARD1 results in decreased HR using the DR-GFP reporter assay.

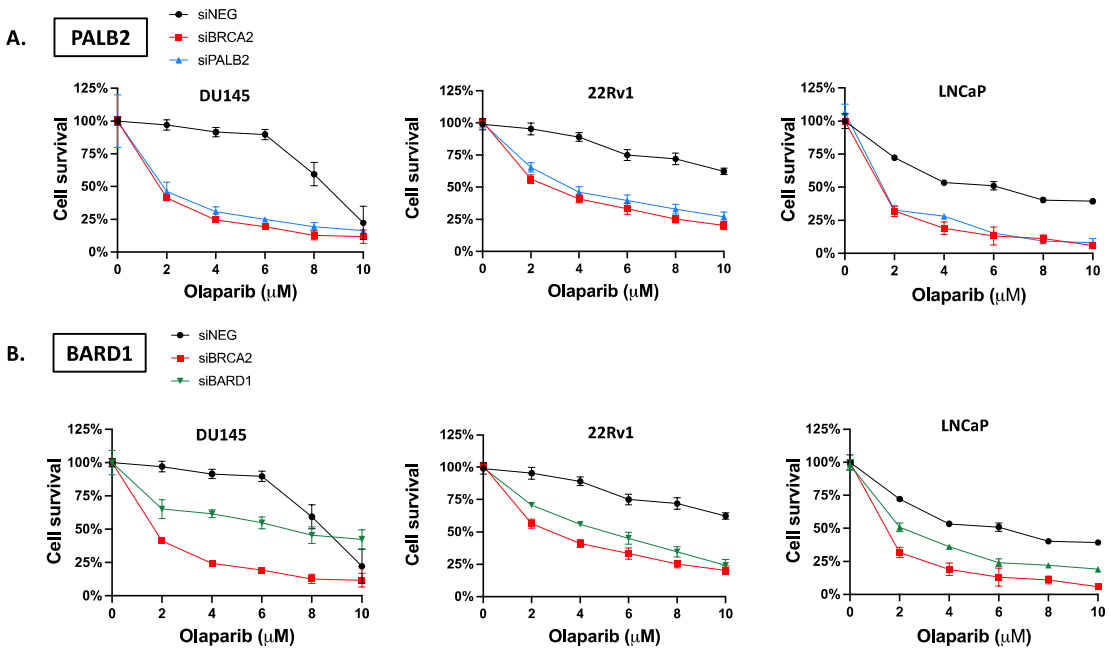


Figure 7: PALB2 or BARD1 loss leads to increased PARP inhibitor sensitivity.

Finally, we have most recently begun to investigate the role of CDK12 loss on DNA damage response and sensitivity to DNA repair-directed agents. CDK12 is a kinase that phosphorylates the C-terminal domain (CTD) of RNA polymerase II to promote transcriptional elongation. We hypothesized that CDK12 loss, which occurs in ~5% of advanced prostate tumors, would result in increased transcriptional pausing leads to replication stress due to collisions between DNA replication machinery and stalled RNA polymerase. To date, we have conflicting data. Acute depletion of CDK12 by siRNA results in an increase in the level of cellular markers of replication stress such as increased phosphorylation of RPA, ATR, and CHK1 by immunofluorescence and/or

immunoblotting as well as increased sensitivity to ATR inhibition. However, we recently acquired a prostate cancer cell in which CDK12 has been deleted by CRISPR, and we are not seeing the same extent of replication stress in this model. We are currently working to resolve these apparent discrepancies.o What opportunities for training and professional development has the project provided?

Shahrzad Rafiei, PhD was a post-doctoral research fellow in the Mouw lab who contributed to aims of this project. She published a first-author paper (Rafiei S, et al. ATM Loss Confers Greater Sensitivity to ATR Inhibition Than PARP Inhibition in Prostate Cancer. Cancer Res. 2020 Jun 1;80(11):2094-2100.)stemming from work related to this project. She also presented her findings as an oral abstract at the 2020 Multi-Institutional Prostate SPORE Retreat, and she won 3rd prize for best oral presentation. She began work related to Major Task #8 prior to leaving the Mouw lab to pursue a full-time position as a Senior Scientist at biotechnology company focused on developing DNA repair protein inhibitors. She was recruited and hired in large part based on the skills that she developed and utilized for this project.

From 10/1/20 through 6/30/21, Kasia Dillon, BS, a research technician in the Mouw lab, committed approximately 50% of her effort to the aims of this proposal. This has allowed her to gain additional skills in prostate cell biology, molecular cloning, and drug sensitivity assays. She used her experience with this project as an example of her research skillset during medical school interviews, and she matriculated to the University of Massachusetts medical school in Fall 2021.

From 6/30/21 to current, Tim Hanlon, BS, a research technician in the Mouw lab, has committed approximately 50% of his effort to the aims of this proposal.

From approximately 3/1/2021 to current, Elizabeth Minten, PhD, a current Harvard Medical School student, has been a part-time contributor to this project. Dr. Minten previously studied BARD1 and BRCA1 interactions during her graduate work, and she has contributed to the aims of this project as part of her medical school thesis work.

From approximately 9/1/21 to current, David Yang, MD, a current clinical fellow in radiation oncology at Dana-Farber/Harvard Cancer Center has been analyzing data from targeted panel sequencing of cfDNA specimens from patients with metastatic prostate cancer. He is presenting results from our pilot studies at the 2022 ASTRO annual meeting. He will assist in analysis of sequencing data from this study, which will help launch his independent research career.

o How were the results disseminated to communities of interest?

Shahrzad presented an oral abstract at 2020 Multi-Institutional Prostate SPORE Retreat entitled "Targeting ATM Deficiency in Prostate Cancer" for which she also won 3rd prize for best oral presentation.

The clinical trial was presented as a "Trial in Progress" at the ASCO Genitourinary Cancers Symposium and at the ASCO Annual Meeting in 2020. This trial was highlighted through UroToday: https://www.urotoday.com/conference-highlights/asco-2020/asco-2020-prostate-cancer/121932-asco-2020-a-phase-ii-study-of-m6620-in-combination-with-carboplatin-compared-with-docetaxel-in-combination-with-carboplatin-in-metastatic-castration-resistant-prostate-cancer.html

An abstract summarizing the preliminary clinical results from the clinical trial was presented as a poster at the 2021 ASCO Annual Meeting.

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

Major Task 1 has been completed.

For Major Task 2, the DNA specimens were shipped from the NCI Biorepository to the Molecular Characterization (MoCha) laboratory for Whole Exome Sequencing (WES) on 3/14/22 and RNA specimens were shipped to the NCLN laboratory at MD Anderson Cancer Center on 3/9/22. WES and RNA-Seq will be completed in the coming months, and WES data will be analyzed in the laboratory of Dr. Eliezer Van Allen, while RNA-Seq data will be analyzed in the laboratory of Dr. Leigh Ellis. Homologous recombination repair deficiency based on WES will be correlated with clinical outcomes (responses to carboplatin + docetaxel; clinical benefit in both arms of the study) per the original grant application.

For Major Task 3, plasma specimens for circulating cell-free DNA analysis from pre-treatment specimens were shipped from the NCI Biorepository to the Broad Institute and underwent ultra-low pass whole genome sequencing with estimates of tumor fraction in these samples depicted in Figure 2. These specimens are currently being sent for targeted panel sequencing as described. Homologous recombination repair deficiency based on cfDNA sequencing will be correlated with clinical outcomes per the original grant application.

For Major Task 4, the MTA is fully executed. Tumor biopsy specimens were shipped from the NCI Biorepository to the Center for DNA Damage and Repair (CDDR) laboratory for RAD51 focus formation, ATM, and phosphor-KAP1 IHC assays. Staining has been completed and analysis is in progress. We will correlate these IHC markers with clinical outcomes.

For Major Task 5, we will perform whole exome sequencing on the post-treatment biopsy specimen that was collected.

For Major Task 6, plasma specimens from end of study specimens were shipped from the NCI Biorepository to the Broad Institute and have undergone ultra-low pass whole genome sequencing per the described workflow. Targeted panel sequencing is pending, and paired analysis compared to pre-treatment specimens will be performed to identify genetic features that emerge over treatment to nominate potential mediators of resistance for further functional analysis.

For Major Task 7 to characterize of VUS in DDR genes, this is pending on sequencing results from Major Task 2 above so will be performed in Year 3 of this award.

For Major Task 8, we will create CHEK2, FANCA, ERCC6, and RAD51C knockout cell lines, and characterize drug sensitivity mediated by loss of these genes.

4. IMPACT:

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

Our published finding that ATM loss confers greater sensitivity to ATR inhibition than PARP inhibition provided functional evidence supporting contemporaneous clinical observations that mCRPC patients with tumor ATM loss had very low response rates to PARP inhibition. Our

findings also provided support for several on-going trials investigating ATR inhibitors in mCRPC patients with tumor ATM loss.

Our data that PALB2 or BARD1 loss is sufficient to confer PARP inhibitor sensitivity in preclinical prostate cancer models (currently under revision for publication) support use of PARP inhibitors in patients with tumor PALB2/BARD1 alterations. Given the relative rarity of these alterations among mCRPC patients, the available clinical trial data did not include sufficient number of PALB2/BARD1-mutant cases to make a statistically powered determination of the potential activity of PARP inhibitors in this population.

Findings from the clinical trial provide important biological insights with regards to drugs that synergize with carboplatin chemotherapy in metastatic castration-resistant prostate cancer (mCRPC), and to guide clinical management and design future clinical trials in these patients. Specifically, our finding that the only responses seen in this study were in patients who received carboplatin and docetaxel was surprising because 1) all patients who received carboplatin plus docetaxel on this trial previously progressed on docetaxel alone and 2) the carboplatin dose given with docetaxel (carboplatin AUC 4) was lower than what was used for carboplatin with berzosertib or carboplatin alone (AUC 5).

There are no prior randomized trials of carboplatin plus docetaxel compared with carboplatin alone, so this trial provides compelling evidence that the combination of carboplatin with docetaxel is favored clinically over carboplatin with berzosertib or carboplatin alone – this finding immediately impacts clinical practice. Our biological understanding of the mechanism by which carboplatin leads to prostate cancer cell death is incomplete: the primary hypothesis of the study, that carboplatin would lead to DNA replication stress (through generation of intra- and inter-strand crosslinks between nucleotide bases) that would then sensitize prostate cancer cells to dying in response to an ATR inhibitor, even in cancers without defects in the DNA damage repair response, was not supported. One explanation for this could be that the ATR inhibitor used in this study, berzosertib, was ineffective at the dose tested. Another explanation is that prior evidence of clinical benefit of carboplatin-containing regimens was due to synergy with docetaxel through mechanisms unrelated to defects in the DNA damage repair response or induction of replication stress. Indeed, a recent study (de Porras et al. Eur Urol. 2020 Nov 2;S0302-2838(20)30778-8.) suggested that docetaxel sensitizes prostate cancer cells to carboplatin by impacting inflammatory pathways that make cells more likely to undergo cell death (apoptosis) in response to carboplatin. These findings are relevant in designing future trials of carboplatin-containing regimens in the future.

o What was the impact on other disciplines?

Nothing to Report.

o What was the impact on technology transfer?

Nothing to Report.

o What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

o Changes in approach and reasons for change

The clinical trial was closed to further enrollment at the time of interim analysis due to futility of the experimental regimen of carboplatin plus berzosertib. However, at least five patients who received carboplatin plus docetaxel achieved a clinical response, and a larger number of patients in both arms of the study experienced clinical benefit as demonstrated by a reduction of PSA by less than 50% or stable disease seen on imaging studies.

These clinical findings suggest the critical importance of the biomarker studies described in this grant application. For example, assessment of HRD by whole exome sequencing from tumor specimens, cfDNA sequencing, and RAD51 focus formation would help us understand whether responses were not seen with carboplatin alone or carboplatin plus berzosertib because by chance none of the patients who received these treatments actually had HRD tumors. Similarly, ATM and phospho-KAP1 IHC will help us understand if any of the patients who received carboplatin plus berzosertib had ATM loss that would be predicted to lead to sensitivity to an ATR inhibitor, or whether no responses were seen due to no patients having ATM deficiency.

We have added RNA-Seq as a planned biomarker study on tumor specimens from this trial. This will help us assess other biomarkers to predict clinical benefit from the carboplatin-based regimens that were investigated. Specifically, we will assess RB pathway loss in collaboration with the laboratory of Dr. Leigh Ellis per a funded RO1 grant. We will also assess activity of the CXCR2/BCL-2 pathway previously reported to be modulated by taxane chemotherapy to sensitize to carboplatin.

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

The Mouw lab was closed completely for approximately 3 months from March through May 2020, meaning that none of the planned functional experiments could be performed during that time period. When the lab re-opened, the lab was operating at ~50% capacity for an additional ~2 months, meaning that progress was much slower than anticipated.

The Center for DNA Damage and Repair laboratory and the Genomics Platform at the Broad Institute of Harvard and MIT were closed for several months due to the COVID-19 pandemic. This delayed the finalization of the material transfer agreements for the tumor and cfDNA specimens. This also delayed the generation of preliminary data in prostate cancer models for RAD51 focus formation and ATM immunohistochemistry shown in Figure 3. The Mouw lab also experienced several important COVID-related delays in receiving necessary reagents, which significantly delayed planned experiments in several instances. This was particularly notable during the Omicron surge in early 2022, when many shipments were delayed and when several lab members were quarantined.

Closure of the Genomics Platform at Broad Institute in 2020 delayed the generation of the preliminary data shown in Figure 1 and receiving biospecimens from this trial. Preparing slides for immunohistochemistry and extraction of nucleic acids at the NCI Biorepository were also delayed due to COVID-19 related staffing shortages.

However, these issues have now been resolved: the plasma specimens for cfDNA analysis have been received and have all undergone ultra-low pass whole genome sequencing. Slides for immunohistochemistry have been received and have undergone staining, with analysis pending. DNA and RNA from pre-treatment tumor biopsy were received by the MoCha laboratory on 3/15/22 and by the NCLN laboratory at MD Anderson Cancer Center on 3/10/22, respectively.

o Changes that had a significant impact on expenditures

The investigators involved in the studies allocated the effort designated to these studies per the original budget to perform the Major Tasks detailed above. However, expenditures related to the analysis of the tumor and cfDNA biospecimens from the clinical trial were delayed due to delay in the material transfer.

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

The clinical trial closed to enrollment after interim analysis due to futility as detailed above. Thus, the number of biospecimens to be analyzed is from 65 patients rather than the 120 as originally projected. This will allow us to perform deeper sequencing on cfDNA specimens as detailed based on preliminary findings from Figure 1 above, and to fund phospho-KAP1 immunohistochemistry as detailed in the amended protocol.

6. PRODUCTS:

o Publications, conference papers, and presentations

Nothing to report

o Journal publications.

Dillon KM, Bekele RT, Sztupinszki Z, Rafiei S, Hanlon T, Szallasi Z, Choudhury A, Mouw KW. PALB2 or BARD1 Loss Confers Homologous Recombination (HR) Deficiency and PARP Inhibitor Sensitivity in Prostate Cancer. Npj Precision Oncology; in revision.

o Other publications, conference papers, and presentations.

Choudhury AD, Xie W, Parikh M, Lee D, Kessler ER, Einstein DJ, Kochupurakkal B, Mouw KW, Van Allen EM, Doyle LA, D'Andrea AD, Taplin ME, Shapiro G. A phase II study of M6620 in combination with carboplatin compared with docetaxel in combination with carboplatin in metastatic castration-resistant prostate cancer. 2020 ASCO Annual Meeting, Abstract TPS5597. 2020, Virtual Meeting. – support from DoD for biomarker studies acknowledged on poster.

Choudhury AD, Xie W, Folefac E, Lee D, Parikh M, Einstein DJ, Kessler ER, Mayer TM, McKay RR, Pace AF, Kochupurakkal B, Mouw KW, Van Allen EM, Kunos C, D'Andrea AD, Taplin ME, Shapiro G. A phase 2 study of berzosertib (M6620) in combination with carboplatin compared with docetaxel in combination with carboplatin in metastatic castration-resistant prostate cancer. 2021 ASCO Annual Meeting, Abstract 5034. 2021, Virtual Meeting. – support from DoD for biomarker studies acknowledged on poster.

Dr. Mouw presented portions of this work in a poster abstract for the 2021 Prostate Cancer Foundation (PCF) Scientific Retreat.

Dr. Minten presented portions of this work in a poster for a Harvard Medical student research symposium in Fall 2021.

o Website(s) or other Internet site(s)

https://www.urotoday.com/conference-highlights/asco-2020/asco-2020-prostate-cancer/121932-asco-2020-a-phase-ii-study-of-m6620-in-combination-with-carboplatin-compared-with-docetaxel-in-combination-with-carboplatin-in-metastatic-castration-resistant-prostate-cancer.html

o Technologies or techniques / Inventions, patent applications, and/or licenses

Nothing to Report

o Other Products

Biospecimen collections

Tumor biopsy specimens and blood specimens for circulating cell-free DNA analysis are stored in the NCI Biorepository.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

o What individuals have worked on the project?

Name:	Atish Choudhury, MD, PhD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-9344-6631
Nearest person month worked:	1.13
Contribution to Project:	Dr. Choudhury is the overall PI of NCI protocol # 10191 and oversees all the translational studies. He is coordinating the biomarker studies on tumor and plasma specimens from this trial and correlating with clinical outcomes. He will also coordinate laboratory collaborations for functional studies of findings from these studies.
Funding Support:	This grant

Name:	Kent Mouw, MD, PhD
Project Role:	Co-Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-7939-7343
Nearest person month worked:	0.48
Contribution to Project:	Dr. Mouw has significant experience in applying cellular and biochemical assays to study the functional implications of DNA repair pathway alterations identified in large sequencing studies. He has worked on prior studies in bladder and prostate cancer, including the functional

	characterization of *ERCC2* mutations identified in cisplatin-response bladder tumors. Dr. Mouw has access to a variety of cutting-edge DNA repair functional assays in the laboratory of Dr. Alan D'Andrea.
Funding Support:	This grant

Name:	Jett Crowdis
Project Role:	Computational Biologist
Researcher Identifier (e.g. ORCID ID):	0000-0003-4777-7303
Nearest person month worked:	1.29
Contribution to Project:	Jett focuses on analysis, method development, and application pertaining to identifying genomic features that correlate with mutational signature analysis of prostate cancers. His tasks also include aggregation and integration of mutational analysis for robust variant detection, as well as sharing of data across platforms.
Funding Support:	This grant

Name:	Tim Hanlon, BS
Project Role:	Research Technician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.0
Contribution to Project:	Mr. Hanlon is paid from a separate grant but some of the cell lines he created and assays he performed for that project were relevant and useful to the aims of this grant.
Funding Support:	Dr. Mouw's Startup funds

Name:	Amruta Samant, MS
Project Role:	Senior Research Technician

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6.00
Contribution to Project:	Ms. Samant focuses on cell-based assays including the creation of DNA repair gene knockout cell lines as well as performing cell proliferation and drug sensitivity assays to compare properties of DNA repair-proficient and -deficient preclinical models.
Funding Support:	This grant

Name:	Bridget Whelpley
Project Role:	Research Data Specialist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.51
Contribution to Project:	Ms. Whelpley is responsible for coordinating data related to this study from the Broad Institute, the Center for DNA Damage and Repair, the MoCha laboratory and the NLCN laboratory.
Funding Support:	This grant

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

CHOUDHURY, ATISH

Previous/Current/Pending Support

Previous:

Nothing in the last 12 months

Active:

PCF-Pfizer Global Challenge Award 04/01/21 – 03/31/24 0.60 CM
Pfizer
A Phase Ia/Ib study of talazoparib in combination with tazemetostat in metastatic castration-resistant prostate cancer (mCRPC)
Goals/Aims: 1) To assess the safety and tolerability of the combination of talazoparib with tazemetostat in mCRPC patients, as well as to establish the Recommended Phase 2 Dose (RP2D); 2) To assess preliminary clinical efficacy of talazoparib with tazemetostat at the RP2D in mCRPC patients as assessed by overall response rate (ORR; PSA reduction by ≥ 50% OR radiographic response by RECIST 1.1)
Role: Principal Investigator
POC: Senior Manager, Outsourcing Lead: Jennifer Barrett; Jennifer.Barrett@pfizer.com

R01CA252468 (Ellis) 06/01/20 – 05/31/22 1.20 CM
NIH/NCI
ATR Dependency as a Novel Therapeutic Target in Lethal RB-deficient Prostate Cancer
Goals/Aims: 1) Validate the ability of DDR kinase targeting to exacerbate DDR deficiency and to generate hypersensitivity in RB-deficient prostate models; 2) Determine the correlation between RB function, HR proficiency and response to M6620+carboplatin and docetaxel+carboplatin in preclinical models and clinical samples; and 3) Evaluate synergy of ATR kinase inhibition, EZH2 inhibition, and immune checkpoint blockade therapy in pre-clinical RB-deficient prostate mouse models.
Role: Co-Investigator
POC: Program Official: Sundaresan Venkatachalam; sundarv@nih.gov

THIS AWARD
W81XWH-20-1-0057 (Choudhury/Mouw) 02/15/20 – 02/14/23 1.20 CM
DoD
Molecular and Genetic Determinants of Response to Carboplatin with or without an ATR Inhibitor (M6620) in mCRPC
Goals/Aims: 1) To correlate genetic and molecular features from pre-treatment tumor biopsy and cfDNA with clinical outcomes for M6620+carboplatin and docetaxel+carboplatin; 2) To discover genetic correlates of resistance to therapy from end-of-study cfDNA specimens and optional biopsies; and 3) To functionally characterize novel genetic alterations identified in pre- and post-treatment specimens using pre-clinical model systems. Role: PI (multi) POC:
Grants Specialist: Michelle Cromwell; michelle.l.cromwell.civ@mail.com;

P01CA228696 (Offit) 09/01/19 – 08/31/25 0.60 CM
NIH/NCI

Targeting the DNA Damage Repair Pathway in Non-Castrate Prostate Cancers
Goals/Aims: 1) To determine the association between long-term clinical outcome and pathogenic germline and somatic variants in DDR genes across different ethnic groups; 2) To develop treatment strategies for patients with germline or somatic alterations in DDR pathways; and 3) To evaluate the functional significance of different alterations in DDR genes.
Role: Co-Investigator
POC: Program Official: Kelly Filipski; kelly.filipski@nih.gov

UM1CA186709 (Shapiro, Flaherty, Kufe) 03/01/19 – 02/29/23 0.60 CM
NIH/NCI
A Phase 2 Study of M6620 in Combination with Carboplatin compared with Docetaxel in Combination with Carboplatin in Metastatic Castration-Resistant Prostate Cancer
Goals/Aims: 1) To correlate pre-treatment DNA damage repair gene mutation status from cfDNA with clinical outcomes for M6620+carboplatin and docetaxel+carboplatin; 2) To correlate a reduction in tumor fraction in cfDNA (as derived from ULP-WGS) from pre- treatment specimen to week 9 specimen with clinical outcomes; 3) To correlate pre-treatment RAD51 focus formation and ATM immunohistochemistry from mandatory pre-treatment tumor biopsies with clinical outcomes
Role: Co-Investigator
POC: Percy Ivy; ivyp@ctep.nci.nih.gov;

IIR-US-2017-4086 11/12/18 – 11/11/22 0.60 CM
Bayer Healthcare Pharmaceuticals, Inc.
Genomic sequencing from circulation free DNA as a predictive biomarker in patients treated with Radium-223
Goals/Aims: 1) Serve as an important proof-of-concept for developing a prostate cancer-specific platform for deep targeted sequencing from circulating free DNA. This study determines whether genomic features detected from cfDNA can predict clinical benefit from Radium-223, which is a radiopharmaceutical that is FDA-approved for prostate cancer based on survival benefit seen in Phase 3 studies. Role: Principal Investigator
POC: Elisa Halbert; Elisa.halbert@bayer.com;

W81XWH1810489 (Huang) 09/29/18 – 09/28/22 0.12 CM
DoD
Investigating Genomic and Immunologic features of Prostate Cancer in African American Men
Goals/Aims: Dr. Choudhury will work with Dr. Huang to analyze cfDNA (Aim 1) in conjunction with a comparison to genomic results from cfDNA in studies at DFCI.
Role: Co-Investigator
POC: Ann Oakenfull; Ann.Oakenfull@ucsf.edu;

IIR-US-2017-4206 06/22/18 – 06/21/22 0.60 CM
Bayer Healthcare Pharmaceuticals, Inc
Genomic alterations in DNA repair genes as predictive biomarkers of the efficacy of Radium-223 with or without pembrolizumab, a humanized monoclonal anti PD-1 antibody
Goals/Aims: 1) To investigate the impact of genomic alterations including those in DNA damage repair pathways on clinical outcomes in patients treated with radium-223 with or without

pembrolizumab; 2) To identify biomarkers of response and to investigate mechanisms of treatment resistance through targeted sequencing of cell free DNA at baseline, on therapy and at the time of disease progression.
Role: Principal Investigator
POC: Elisa Halbert; Elisa.halbert@bayer.com;

Pending:

962681 07/01/22 – 06/30/25 1.80 CM
Damon Runyon Cancer Research Foundation
Molecular Determinants of Response and Resistance to Talazoparib with Tazemetostat in mCRPC
Goals/Aims: 1) To characterize molecular changes in blood and tissue biospecimens from patients treated with the combination of talazoparib and tazemetostat; 2) To identify biomarkers of response and resistance to the combination of talazoparib and tazemetostat.
Role: Principal Investigator
POC: Yung Lie; yung.lie@damonrunyon.org;

R01 TBD (Penney, Tyekucheva) 07/01/22 – 06/30/27 1.20 CM
NIH/NCI
Spatial heterogeneity of gene expression within the prostate microenvironment and aggressive prostate cancer
Goals/Aims: In this proposal, we will explore the transcriptomic profile of the prostate tumor microenvironment in two different but interrelated clinical contexts: across tumor grade (Gleason score) and across responses to neoadjuvant androgen deprivation therapy (ADT)
Role: Co-Investigator
POC: Crystal Wolfrey; wolfreyc@mail.nih.gov;

PC210551 09/30/22 - 09/29/26 0.60 CM
DoD
Prostate cancer clinical trials consortium: Dana-Farber
Goals/Aims: Develop and enhance collaborations and resources necessary for a network of organizations to rapidly execute Phase II or Phase II-linked Phase I (Phase I/II) prostate cancer clinical trial
Role: Co-Investigator
POC: Joshua D. McKean; joshua.d.mckean3.civ@mail.mil; 301- 682-5507

R21CA277462 12/01/22 – 11/30/24 1.20 CM
NIH/NCI
Immunogenomic profiling for abemaciclib +/- atezolizumab in mCRPC
Goals/Aims: 1) To characterize change in immune infiltrate for patients treated with abemaciclib alone vs. abemaciclib with atezolizumab; 2) To genetically profile circulating cell- free DNA (cfDNA) from patients treated with abemaciclib
Role: Principal Investigator
POC: Crystal Wolfrey; wolfreyc@mail.nih.gov;

MOUW, KENT
Previous/Current/Pending Support

PREVIOUS:

(ended)
Broad Institute/Novo Ventures Joint Seed Grant 08/01/2019–01/31/2022
annual direct costs 0.12 calendar months* *Inhibition of ERCC2 to Synergize with Cisplatin for Treatment of Urothelial Carcinoma*
The major goal of this project is to develop a small molecular inhibitor of ERCC2 ATPase function.
Role: Co-PI
Overlap: This effort is complementary to the K08 because it involves parallel biochemical assays as are proposed for the ERCC2 mutants being analyzed in the K08. No salary support is being received and there are no budgetary overlaps.
POC: Nabil A. Khan
Contracts and Research Agreements Administrator, Broad Institute
Office of Sponsored Research

(ended)
DOD CA160312 (PI: Van Allen) 9/30/2017–9/30/2021 NCE 0.48 calendar months
Total Cost
Precision Medicine in Platinum-Treated Lethal Bladder Cancer
The major goal of this study is to validate potential biomarkers predictive of the clinical activity of cisplatin-based chemotherapy for bladder cancer and to identify the biological determinants underlying vascular endothelial growth factor (VEGF) pathway dependency.
Role: Co-Investigator
Overlap: This effort is complementary to the K08 because the same assays will be used to profile ERCC2 mutations identified from sequencing of bladder tumors funded by DOD and K08 grants. No salary support is being received and there are no budgetary overlaps.
POC:
Jodi Cardoza
Grant Specialist
USAMRAA
820 Chandler Street
Fort Detrick, MD 21702

CURRENT:

CAMS 9/1/2017–8/31/2022 0.6 calendar months*
Burroughs Wellcome Fund Total Cost
Investigating the effect of ERCC2 mutations on DNA repair capacity and chemo-radiotherapy response in muscle-invasive bladder cancer
The major goal is to study the mechanisms through which somatic *ERCC2* mutations impact DNA repair and treatment sensitivity in bladder cancer using a combination of cellular, biochemical, and genomic approaches.
Role: PI

Overlap: This effort is complementary to the K08 because BW funding will be used to supplement funding for sequencing of clinical bladder samples outlined in Aim #3. No salary support is being received and there are no budgetary overlaps
POC:
Rolly L. Simpson Jr.
Senior Program Officer
21 TW Alexander Drive
P O Box 13901
Research Triangle Park, NC 27709
Phone:

5K08CA219504-03 7/1/2017–6/30/2022 9.0 calendar months
Total Cost
Investigating the effect of ERCC2 mutations on DNA repair capacity and chemo-radiotherapy response in muscle-invasive bladder cancer
The specific aims of this study are to: (1) dissect the functional landscape of ERCC2 mutations in bladder cancer, (2) investigate the mechanistic underpinnings of ERCC2 mutations, and (3) define the association between ERCC2 mutations and chemoradiotherapy response in bladder cancer.
Role: PI
POC:
Justin Birken
Grants Management Specialist
Birkenjg@mail.nih.gov
Phone:

(this award)
DoD (Choudhury/Mouw) 02/15/2020-02/14/2023 0.48 calendar months
PC190196 Total Cost
Molecular and genetic determinants of response to carboplatin with or without an ATR inhibitor (M6620) in mCRPC
Aims:
1) to correlate genetic and molecular features from pre-treatment tumor biopsy and cfDNA with clinical outcomes for M6620+carboplatin and docetaxel+carboplatin
2) to discover genetic correlates of resistance to therapy from end-of-study cfDNA specimens and optional tumor biopsies
3) to functionally characterize novel genetic alterations identified in pre- and post-treatment specimens using pre-clinical model systems.
Role: Co-PI
Overlap: None
POC:
Joshua Mckean
Grants Officer
TEL:

1U01CA260369-01 (PI: Abbosh) 03/01/21–02/28/26 0.3 calendar months*
Total cost
Optimization of urinary DNA deep sequencing tests to enhance clinical staging of bladder cancer patients
Role: Subcontract PI

Overlap: The proposed work is complementary to the K08 because it utilizes the same specimens as will be analyzed for work proposed in the K08.
POC: TBD

1R01CA252468-01 (PI: Ellis) 07/01/2020–06/30/2025 0.24 calendar months *
Total Cost: (complementary effort)
ATR Dependency as a Novel Therapeutic Target in Lethal RB Deficient Prostate Cancer
Major Goals: To investigate DNA repair function and sensitivity to DDR kinase inhibitors in RB-deficient prostate cancer and investigate therapeutic approaches that combine DDR kinase inhibition with novel agents for treatment of advanced prostate cancer.
Role: Co-Investigator
Overlap: The proposed work is complementary to the K08 because it will leverage similar tools to create DNA repair deficient cell lines.
POC: TBD

1R21CA263130-01 (PI: Mouw) 07/01/21-06/30/2022 0.6 calendar months*
total cost
Targeting the DNA Damage Response in CDK12-Mutant Prostate Cancer
Major Goals: The major goal of this project is to explore whether CDK12-mutant prostate cancers are sensitive to inhibitors of the ATR kinase
Role: PI
Overlap: None
Bryann Benton
Grants Management Specialist
NATIONAL CANCER INSTITUTE
bentonb@mail.nih.gov

<u>PENDING</u>

R01 (PI: Mouw) 07/01/22-06/30/27 2.4 calendar months
total cost
Project Title: Targeting Nucleotide Excision Repair Deficiency in Bladder Cancer
Major Goals: The major goals of this project is to dissect the cellular mechanisms that contribute to the unique properties of NER deficient tumors and to define the impact of NER deficiency on CRT response.
Role: PI
Overlap: None
POC: TBD

Please Note: If pending application is funded, Dr. Mouw will work with the sponsoring agencies to adjust effort accordingly, so that his effort will not exceed 100%.

ELIEZER VAN ALLEN, MD
PREVIOUS/CURRENT/PENDING SUPPORT

PREVIOUS

Mark Foundation (Jian Ma) 10/01/2019-04/31/2021
0.05 CM
Carnegie Mellon University Sub
Characterization Of Non-Coding Driver Mutations Based on the 3D Cancer Genome Structure
We will develop computational methodology for identification of noncoding mutations in cancer genomes. We will collaborate with the Ma Lab to map these candidates to 3D structures using multi-modal data sets from experimental systems.
Role: Co-Investigator
POC: grants@themarkfoundation.org
Overlap: N/A

Novartis 01/01/2018 – 06/31/2021
0.12 CM
Novartis DDP
Characterizing and Overcoming Genomic Mechanisms of Resistance to PD-1 Inhibitors in Melanoma
Specific Aims: Aim 1. To characterize acquired and intrinsic resistance to standard of care immune checkpoint inhibitors. Aim 2. To identify genomic drivers of acquired resistance to immune checkpoint inhibitors in GU/melanoma.
Role: Co-Principal Investigator
POC: Sylvia Lin, Grant Manager; Sylvia_Lin@dfci.harvard.edu
Overlap: N/A

W81XWH-18-1-0200 09/30/2018 – 09/14/2021
0.36 CM
DoD Idea Award (PI: Schultz)
Mutational Landscape of the Y Chromosome and Prostate Cancer
The Van Allen lab would perform genomic and transcriptome analysis of chromosome Y events in prostate cancer, integrate analyses with preclinical work proposed in this project, and work collaboratively with the institutions involved to enable the computational components of this project.
Role: Subcontract PI
POC: Nikolaus Schultz; schultzn@mskcc.org;
Overlap: N/A

Mark Foundation (Michael Schatz) 10/01/2019 - 09/30/2021 (NCE)
0.12 CM
Johns Hopkins University Sub
Analysis of Cryptic Variants in Cancer Genomes using Long Read Sequencing
We will share DNA specimens from our outlier cancer families project with the Schatz Lab to perform long read genome sequencing. We will then collaborate to identify structural variants that may contribute to the familial inheritance phenotypes.
Role: Co-Investigator

POC: grants@themarkfoundation.org
Overlap: N/A

Prostate Cancer Foundation and V Foundation (Van Allen) 10/01/2017 - 09/01/2021 (NCE)
0.00 CM*
PCF-TVF Challenge Award
Exploiting DNA Repair Defects in Metastatic Prostate Cancer to Promote Immunotherapeutic Responses
The purpose of the grant program is to support cancer research projects and related programs that are designated to change the course of cancer.
Role: Principal Investigator
POC: applications@pcf.org
Overlap: N/A

DF/HCC Kidney Cancer SPORE (McDermott/Kaelin) 09/01/2020 – 08/31/2021
0.06 CM
NIH/NCI
Dissecting the Spatial Patterns of ccRCC Genomic Subtypes with Deep Learning
In this project, we will 1) Determine the latent representations of ccRCC spatial configurations within and between genomic subtypes and 2) Develop deep learning models to predict key clinical outcomes directly from ccRCC histopathology images. Broadly, these efforts represent emerging opportunities at the intersection of genomics, multimodal histopathology, and deep learning to advance biological insights and predictive modeling in ccRCC.
Role: Co-Investigator
POC: Tara Johnston; Email: tjohnst1@bidmc.harvard.edu
Overlap: N/A

W81XWH-18-1-0480 (Choueiri/ Signoretti) 09/01/2018 - 08/31/2021
0.21 CM
DoD/KCRP TRPA
Predictive Biomarkers for Nivoiumab Treatment In Metastatic Renal Cell Carcinoma
Aim 1 will focus on the validation of blood-based biomarkers of response to nivolumab in metastatic ccRCC. Aim 1a: To validate the impact of nivolumab therapy on kynurenine, and to examine whether changes in kynurenine levels correlate with nivolumab benefit.
Aim 1b. To validate the negative predictive value of serum adenosine in patients treated with nivolumab. Aim 2 will focus on the validation of tissue-based biomarkers of response to nivolumab in metastatic ccRCC. Aim 2a: To validate the predictive value of biomarkers expression by immunostaining assays in patients treated with nivolumab.
Aim 2b: To validate the predictive value of tumor genetic alterations in patients treated with nivolumab. Aim 2c: To investigate the predictive value of T-effector- and myeloid-associated gene signatures in patients treated with nivolumab (Exploratory Aim).
Role: Co-Investigator
POC: Amanda Carrera, Grants Specialist; Amanda.c.carrera.civ.@mail.mil; 301-619-2108
Overlap: N/A

R21CA242861 (Van Allen) 07/01/2019 - 12/31/2021 (NCE)
0.06 CM
NIH/NCI

A Statistical Framework to Systematically Characterize Cancer Driver Mutations in Noncoding Genomic Regions
Overall, this proposal will enable a systematic interrogation of the landscape of noncoding driver mutations and assess the impact of different mutational processes on the clinical response to immune checkpoint therapies. Aim 1: To define the landscape of noncoding cancer driver mutations using nucleotide context. Aim 2: To determine the impact of passenger mutation distribution patterns on neoantigen development and response to cancer immunotherapy.
Role: PI
POC: Justin Birken, GMS; birkenjg@mail.nih.gov;
Overlap: N/A

CURRENT

R01CA227388 (Van Allen) 06/01/2018 – 05/31/2023
2.28 CM
NIH/NCI
Integrative Somatic and Germline Computational Biology to Redefine Clinical Actionability in Solid Tumors
Aim 1: To determine inherited cancer risk in solid tumors through integrative computational biology. Aim 2: To evaluate the impact of somatic and germline interactions on DNA repair defects and response to platinum--based chemotherapies in solid tumors. Aim 3: To identify somatic and germline features that coordinate to alter the immune microenvironment and impact selective response to immune checkpoint blockade in solid tumors.
Role: PI
POC: Jacquelyn Saval, GMS; Boudejedaj@mail.nih.gov;
Overlap: None.

R37CA222574 (Van Allen) 02/01/2018 – 01/31/2023
2.28 CM
NIH/NCI
Molecular Origins and Evolution To Chemoresistance In Germ Cell Tumors
Aim 1: To define the genetic defects associated with reciprocal loss of heterozygosity in primary germ cell tumors. Aim 2: To identify the molecular features of tumor evolution leading to chemoresistant germ cell tumors. Aim 3: To assess the clinical utility of pluripotency markers as prognostic for GCT outcomes.
Role: Principal Investigator
POC: Ashley Salo, GMS; ashley.salo@nih.gov;
Overlap: None.

U01CA233100 (Fong/Van Allen) 09/19/2018 – 08/31/2023
1.20 CM
NIH/NCI
Molecular And Immune Drivers of Immunotherapy Responsiveness in Prostate Cancer
Aim 1: To define the systemic and infiltrating immune responses in prostate cancer associated with response to checkpoint blockade. Aim 2: To determine the immunologic impact of chromatin dysregulation and inhibition in prostate cancer. Aim 3: To establish the impact of existing DNA damaging agents for sensitizing prostate cancer to immune checkpoint blockade.
Role: PI (MPI – Contact)
POC: Justin Birken, GMS; birkenjg@mail.nih.gov;
Overlap: None.

U24CA224316 (PI: Liu/Cerami) 09/30/2017 – 06/30/2022
0.36 CM
NIH/NCI
Cancer Immunologic Data Commons (CIDC)
Goals: 1) coordinate with the CIMAC and Laboratory Coordinating Committee (LCC) to harmonize assay protocols and data format standards, 2) develop a centralized data repository and management system, and coordinate CIMAC data submission to the CIDC, 3) Develop uniform bioinformatics processing pipelines and computing infrastructure for computation intensive analyses for the CIMACs and the larger research community, 4) Provide bioinformatics algorithms to enable integrative and correlative analysis of CIMAC as well as integrate other accessible databases and resources for biomarker discovery, 5) Develop centralized role-based data access functions with advanced programming interface to enable sharing of CIMAC data, 6) Develop interactive web visualization functions to enable investigators and the immunology communities to examine the CIMAC data, and 7) Coordinate within the CIMACs-CIDC Network logistic and scientific activities for biomarker discovery and validation.
Role: Co-Investigator
POC: Magdalena Thurin, PO; thurinm@mail.nih.gov
Overlap: None.

U2CCA233195 (Johnson) 09/24/2018 – 08/31/2023
0.12 CM
NIH/NCI
The Cellular Geography of Therapeutic Resistance in Cancer: Biospecimen Unit
Aim 1. Create an adaptive power analysis paradigm for tumor cell atlases; Aim 2. Develop a pre-processing and analysis computational workflow for each data modality; Aim 3. Determine the cell intrinsic and extrinsic features relevant to tumors
Role: Project Co-Lead
POC: Justin Birken, GMS; birkenjg@mail.nih.gov;
Overlap: None.

W81XWH-17-1-0545 09/15/2017 – 06/14/2022 (NCE)
0.24 CM
DoD (Rosenberg/Van Allen)
Precision Medicine in Platinum-Treated Lethal Bladder Cancer
Specific Aims: To determine (1) the association between somatic alterations in ERCC2 and other DDR genes and clinical outcomes of patients treated with gemcitabine and cisplatin on CALGB 90601, (2) the impact of intrinsic tumor subtypes on response to chemotherapy and VEGFR blockade, and (3) the underlying biology of extreme sensitivity to gemcitabine and cisplatin (with or without bevacizumab) in outlier responses through integrated molecular and functional analyses.
Role: Partnering PI
POC: Jodi Cardoza, Grants Specialist; Jodi.l.cardoza.civ@mail.mil;
Overlap: None.

Prostate Cancer Foundation (Van Allen) 10/11/2019-10/10/2022 (NCE)
0.28 CM
PCF Challenge Award
A Genomics-Guided Clinical Interpretation and Translational Discovery Engine for Prostate Cancer

The specific aims of this proposal are: 1) To develop deep learning algorithms for molecular discovery in large harmonized cohorts of primary and metastatic prostate cancer; 2) To predict clinical outcomes for MPC patients using natural language processing and deep learning models applied to both clinical text and molecular data; and 3) To develop a prostate cancer clinical trial decision support framework and determine the feasibility of delivering molecular data for MPC patients at the point of care.
Role: Principal Investigator
POC: applications@pcf.org
Overlap: None.

P01 CA228696-01A1 (MPI: Offit/Pomerantz) 09/01/2019 - 08/31/2025
0.60 CM
NCI
Genomics Core - The Impact of DNA Damage Repair Abnormalities in Prostate Cancer
Aberrations in genes that help repair damaged DNA are seen in 20-25% of men with metastatic castration-resistant prostate cancer, the lethal form of prostate cancer. We have assembled a multidisciplinary team to increase our understanding of the role the spectrum of DNA repair aberrations play in prostate cancer.
Role: Co-Leader
POC: T Gussaki, Grant Manager; GussakiT@mskcc.org
Overlap: None.

Mark Foundation (Van Allen) 01/01/2020 - 12/31/2022
0.60 CM
Emerging Leader Award
Convergence of Machine Learning and Translational Genomics for Prostate Cancer Precision Medicine
The specific aims of this proposal are: 1) To develop deep learning algorithms for molecular discovery in large harmonized cohorts of primary and metastatic prostate cancer; 2) To predict clinical outcomes for MPC patients using natural language processing and deep learning models applied to both clinical text and molecular data; and 3) To develop a prostate cancer clinical trial decision support framework and determine the feasibility of delivering molecular data for MPC patients at the point of care.
Role: PI
POC: grants@themarkfoundation.org
Overlap: None.

This award
W81XWH-20-1-0057 (Choudhury/Mouw) 02/15/2020 - 02/14/2023
0.12 CM
Department of Defense
Molecular and Genetic Determinants of Response to Carboplatin With or Without an ATR Inhibitor (M6620) in mCRPC
Aims: 1) to correlate genetic and molecular features from pre-treatment tumor biopsy and cfDNA with clinical outcomes for M6620+carboplatin and docetaxel+carboplatin; 2) to discover genetic correlates of resistance to therapy from end-of-study cfDNA specimens and optional tumor biopsies; 3) to functionally characterize novel genetic alterations identified in pre- and post-treatment specimens using pre-clinical model systems.
Role: Co-Investigator

POC: Michelle Cromwell, Grants Management Specialist, USAMRAA, 820 Chandler Street, Building 817A, Frederick, MD 21702; michelle.l.cromwell.civ@mail.com; Overlap: N/A

U2C CA252974-01 (Wagle) 09/01/2020 - 08/31/2025
0.60 CM
NIH – Broad Institute Billing Agreement (TC All Years – DFCI) Count Me In: Partnering with Patients to Define the Clinical and Genomic Landscape of Rare Aggressive Sarcomas in Children and Adults
Rare cancers comprise over 25% of tumors in U.S. adults, but due to low incidence and geographically dispersed patient populations, they are challenging to study, leading to significant unmet clinical needs. This proposal will form a Research Center that will directly engage patients with two such rare cancers – osteosarcoma and leiomyosarcoma – as partners in research in order to generate a large-shared database of clinical, genomic, molecular, and patient reported data. We hope that this work can accelerate discoveries that drive novel treatment strategies, new clinical trials, and new standards of care, and also serve as a model for patient partnered research in other cancer types and patient communities.
Role: Co-Investigator
POC: Elizabeth Gillanders, Program Official, Email lgilland@mail.nih.gov
Overlap: None.

NIH/NCI (Sweeney) 05/01/2020 –04/30/2025
0.48 CM
R01CA238020
Comprehensive Genomic Profiling of Aggressive Hormone Sensitive Prostate Cancer
Aims: Aim 1: To define the impact of tumor suppressor gene (TSG) alterations (TP53, PTEN, RB1) on clinical outcomes of patients with mHSPC treated with ADT or ADT plus docetaxel in the CHAARTED trial. Aim 2: To determine whether transcriptional profiles are associated with poor prognostic clinical features and/or TSG alterations and result in more accurate prognostication of outcomes with ADT or ADT plus docetaxel. Aim 3: To determine whether transcriptional profiles result in more accurate predictive models for benefit from adding docetaxel to ADT.
Role: Co-Investigator
POC: Tawnya C. McKee, Program Officer, mckeeta@mail.nih.gov
Overlap: None.

NIH/NCI CTEP UM1 CA186709 03/13/2014 – 02/28/2023
0.24 CM
(Shapiro, G., Kufe, D., Flaherty, K.)
Dana-Farber/Harvard Cancer Center Experimental Therapeutics Clinical Trials Network Site (DF/HCC ETCTN Site)
Specific Aims are: (1) to propose novel clinical trials based on sound preclinical evidence and rationale that advance the clinical development of CTEP IND agents; (2) to develop early phase clinical trials of CTEP IND agents as monotherapies or in rational combinations that include safety, pharmacokinetic, translational and efficacy endpoints across a broad range of cancer types; (3) to incorporate validated integral and integrated biomarker assays and exploratory biomarkers in clinical study designs that examine proof-of-principle evidence of therapeutic activity in selected patient populations, proof-of-mechanism evidence of target engagement, as well as determinants of response, pathway adaptation and intrinsic resistance along with mechanisms of acquired resistance; (4) to activate trials with CTEP IND agents in compliance with guidelines established by

the Operational Efficiency Working Group; (5) to efficiently conduct, complete and report on clinical trial outcomes in a timely fashion by working with other ETCTN sites; (6) to collaborate with other NCI-supported programs, including DF/HCC SPOREs; (7) to utilize NCI resources including the Molecular Characterization Laboratory (MoCha), the Pharmacodynamic Assay Development and Implementation Section (PADIS), the Drug Resistance and Sensitivity Network (DRSN), Cancer Immune Monitoring and Analysis Centers (CIMACs), the Patient-Derived Xenograft Development and Trial Centers Research Network (PDXNet), and the National Clinical Laboratory Network; (8) to extend ETCTN trials to rare and underserved populations; and (9) to provide mentorship to early career clinical and translational investigators in developmental therapeutics and in early phase clinical trial design and conduct.
Role: Co-Investigator
POC: S. Percy Ivy, ivyp@ctep.nci.nih.gov
Overlap: None.

NIH/NCI CTEP UM1 CA186709 09/04/2014 – 02/28/2023
0.24 CM
(Shapiro, G., Kufe, D., Flaherty, K.)
DFCI-BWH-Broad Institute Molecular/Biomarker Characterization Hub (Supplement)
Major Goals: Specific Aim 1: Provide molecular analyses for ETCTN-wide clinical trials that include integral and exploratory biomarkers or other molecular determinants of response and resistance A. Conduct CLIA-grade tumor genomic profiling of at least 120-200 patient tumor specimens from ETCTN Trials B. Perform comprehensive genomic characterization of selected paired tumor specimens obtained prior to treatment and following relapse. Specific Aim 2: Participate in ETCTN-wide consortium activities to assist in the clinical evaluation of molecular variants and driver mutations
Status of Support: Active
Role: Co-Investigator
POC: S. Percy Ivy, ivyp@ctep.nci.nih.gov
Overlap: None.

RTFCCR-MRA Established Investigator Award 06/01/2021 – 05/31/2023
0.24 CM
Melanoma Research Alliance
Dissecting The Impact of Noncoding Structural Variation In Melanoma Genomes
Aim 1: To harmonize and uniformly analyze of the largest cohort of melanoma whole genome data in a cloud environment; Aim 2: To elucidate the origins of structural variants relative to known driver mutations and mutational processes; Aim 3: To determine the somatic noncoding structural lesions that impact three-dimensional genome architecture.
Role: PI
POC: Kristen Mueller; Email: kmueller@curemelanoma.org
Overlap: None.

DF/HCC Kidney Cancer SPORE (McDermott/Kaelin) 09/01/2021 – 08/31/2022
0.12 CM
NIH/NCI

Dissecting The Spatial Patterns of Ccrcc Molecular Subtypes and Micro-Environments with Deep Learning

In this project, we will expand on our prior work and: 1) Determine the latent spatial representations of ccRCC transcriptional programs in histopathology images; and 2) Develop deep learning models that predict clinical outcomes from tumor, immune, and stromal representations in ccRCC histopathology images. Broadly, these efforts represent emerging opportunities at the intersection of genomics, multimodal histopathology, and deep learning to advance biological insights and predictive modeling in ccRCC.
Role: Co-Investigator
POC: Tara Johnston; Email: tjohnst1@bidmc.harvard.edu
Overlap: None

Brown Performance Group 06/04/2018 – 06/01/2022
0.12 CM
Deep Learning Models to Accelerate Translational
Cancer Genomics
Aim 1: To develop a biologically informed machine learning model for outcome prediction and hypothesis generation using cancer genomics. Aim2: To apply P-net to translational and clinical cancer genomics challenges and identify novel predictive markers.
Role: PI
POC: Audrey Cook acook@brownphilanthropy.com
Overlap: None.

7157481-5500001597/DFCI # SRA-21-0642 02/01/2021 – 07/31/2023
0.30 CM
Broad Institute (Mouw)
Dissecting the Mechanism of Action of PD1 Blockade in Endometrial Carcinoma Utilizing Novel Organoid Co-Cultures
Major Goals: Objective: Develop a robust screening assay to enable identification of ERCC2 ATPase inhibitors
Key Activities: 1) Perform pilot screen to validate biochemical assay and characterize hits using cell-based assay; 2) Screen up to 25,000 compounds in biochemical assay to determine assay robustness and target ligandability; 3) Validate hits to identify their mechanism of action (ATP competition, helicase activity, direct binding); 4) Test hits from biochemical screening for inhibition of ERCC2 NER activity in cell-based
assay
Role: Co-Investigator
POC: Hannah Kim, Business Manager, Large Alliances; Hannah@broadinstitute.org
Overlap: None

22001-01 01/01/2022 – 06/30/2024
0.30 CM
Novartis Drug Discovery and Translational Research
Program DDTRP (Van Allen)
Title: Dissecting the Role of Gal-9 in Immunotherapy Resistance
Major Goals: Aim 1: Evaluate protein expression of Gal-9 in the RCC tumor-immune microenvironment and assess association with clinical outcomes. Aim 2: Assess Gal-9-mediated immune cell inhibition using RCC model systems.
Role: Principal Investigator
POC: Henry W. Long, PhD, Scientific Coordinator; Phone:
Overlap: None

W81XWH-19-PCRP-EIRA 03/01/2020 – 02/28/2023
0.00 CM
Department of Defense (Hamid)
PC190530 PAIR Genomic Predictors of Clinical Outcomes and Benefit of (Chemo) Hormonal Therapy in Metastatic Hormone Sensitive Prostate Cancer
Major Goals: The aims of this project are: Aim 1A: to determine whether TSG alterations are prognostic and/or predictive of outcome with ADT or ADT plus docetaxel in the CHAARTED trial, Aim 1B: to determine whether TSG alterations are associated with clinicopathologic features of mHSPC, and assess both prognostic and predictive associations in multivariable models in the CHAARTED trial, Aim 2: to validate the prognostic and predictive role of TSG alterations in clinicogenomic models of mHSPC in patients treated with ADT or ADT plus docetaxel in the STAMPEDE trial.
Role: Co-Investigator
POC:
Overlap: N/A

PENDING

KC210042 (AlDubayan) 07/01/2022 – 06/30/2025
0.0 CM
Department of Defense Idea Development Award
Dissecting Germline Genetic Mediators of Clinical Response to Immune Checkpoint Blockade in Kidney Cancer
In this study, we hypothesize that greater tumor sensitivity and better clinical response to immune checkpoint inhibitors in RCC are influenced by germline genetic features that can be uncovered through an integrative, multimodal computational analysis framework of the germline genomes of clinically annotated ICB-treated RCC cohorts. Aim 1: To construct predictive models of tumor sensitivity to ICB in RCC using common germline variation in the immune-related pathways; Aim 2: To investigate rare germline loss-of-function (LOF) variants as molecular mediators of greater response to therapy in ICB-treated RCC cohorts; Aim 3: To examine the transcriptional activity of germline non-coding elements in ICB-treated RCC patients using a multi-modal genomic and transcriptomic characterization approach.
Role: Career Guide/Mentor
POC: TBD
Overlap: None.

W81XWH-21-PCRP-DSA (Van Allen) 04/01/2022 – 03/31/2025
0.60 CM
Department of Defense
Interrogating Metastatic Prostate Cancer Biological and Clinical Trajectories Through Integrative Data Science
Major Goals: Aim 1: Define the integrative genomic features that mediate metastatic prostate cancer using biologically guided neural networks; Aim 2: Determine the tumor-intrinsic and immune microenvironmental transcriptional programs operant in metastatic prostate cancer; Aim 3: Apply deep neural networks to integrated structured and unstructured EHR data to derive longitudinal clinical representations of MPC trajectories.
Role: Partnering PI

POC: Jason Wong, Ph.D., Science Officer, Prostate Cancer Research Program (PCRP), Goldbelt Frontier, LLC, Supporting the Congressionally Directed Medical Research Programs (CDMRP), USAMRDC; Phone: ; Email: jason.wong5.ctr@mail.mil
Overlap: None.

Movember Foundation 10/01/2021 – 09/30/2022
0.06 CM Movember GAP5 Award – Broad Institute Subcontract
Testicular Cancer Translational Research Project (GAP5)
Aim #1: Establish a secure platform for identifying, collecting and analyzing clinical and biospecimen data to answer the above clinical question and to ensure this resource is available for future translational use. Aim #2: Determine if there are germline genetic features associated with resistance to cisplatin-based chemotherapy. Aim #3: To determine the association between putative molecular tumor tissue markers (DNA, mRNA, miRNA) and resistance to cisplatin-based chemotherapy.
Role: Principal Investigator
POC: Sam Gledhill, Global Director, Digital Health, Movember Foundation; Email: Sam@Movember.com
Overlap: None.

R01 CA272657-01 (Mouw) 07/01/2022 – 06/30/2028
0.00 CM
NIH/NCI
Project Title: Targeting Nucleotide Excision Repair Deficiency to Improve Bladder Sparing Treatment for Muscle Invasive Bladder Cancer
Aim: To define the impact of NER deficiency induced by ERCC2 mutations on bladder tumor properties and on response to clinically relevant bladder-sparing CRT regimens by integrating genomic and clinical data from clinical MIBC cohorts with functional data from novel NER-proficient and NER-deficient preclinical models
Role: Other Significant Contributor
POC: TBD
Overlap: None.

Overlap:
Should all pending proposals be funded, effort will be adjusted accordingly to not exceed 12CM.

OTHER AFFILIATIONS AND RESOURCES

IN-KIND
Summary of In-Kind Contribution: Imam Adbulrahman Bin Fisal University in Saudi Arabia. Gift is to support breast cancer research.
Status of Support: Active
Primary Place of Performance: Dana Farber Cancer Institute
Project/Proposal Start and End Date (MM/YYYY) (if available):01/01/2020-09/31/2021
Person Months (Calendar/Academic/Summer) per budget period: N/A
Estimated Dollar Value of In-Kind Information:
No financial support for Dr. Van Allen

Industry Sponsored Clinical Trials
Funding and effort dependent on accruals for all project listed below.

DF/HCC - Genetech (Choueiri) 03/30/2018-03/29/2024 0.0 CM*
Clinical Trial 15-592 A Phase II
We are performing correlative molecular analyses on samples from these clinical trials for biological discovery and biomarker development that pertain to the therapeutics and clinical contexts being investigated.
Role: Co-Investigator

DF/HCC Rare GU (Choueiri) 05/09/2018-05/08/2024 0.0 CM*
Clinical Trial 17-423-B Phase II
We are performing correlative molecular analyses on samples from these clinical trials for biological discovery and biomarker development that pertain to the therapeutics and clinical contexts being investigated.
Role: Co-Investigator

DF/HCC Omnivore (Choueiri) 06/19/2018-06/18/2024 0.0 CM*
Clinical Trial 17-064-B
We are performing correlative molecular analyses on samples from these clinical trials for biological discovery and biomarker development that pertain to the therapeutics and clinical contexts being investigated.
Role: Co-Investigator

BMS (Tolaney, Sara, Van Allen) 08/26/2017 – 12/31/2022 0.0 CM*
Clinical Trial OT123-324 TM 188 PA 35
Understanding Response; and Resistance to PD-1 Inhibition in Triple Negative Breast Cancer (TNBC) by Analyzing Extremes of Response
The purpose of this research is to identify tumor and immune cell genomic and transcriptome signatures and biomarkers associated with response and resistance to carboplatin and nivolumab among metastatic TNBC patients. This study will investigate whole exome/transcriptome sequencing and single-cell RNA sequencing, multiplex immunohistochemistry, mass cytometry, T-cell receptor profiling, and cytokine levels.
POC: Sharon Hanlon, Group Director, CEE, Global Clinical Operations
Role: Co-PI

o What other organizations were involved as partners?

1) Organization Name: NCI Biorepository

Location of Organization: Columbus, OH

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

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);

2) Organization Name: NCI Molecular Characterization (MoCha) laboratory

Location of Organization: Frederick, MD

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

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);

3) Organization Name: Broad Institute of MIT and Harvard

Location of Organization: Cambridge, MA

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

Facilities (e.g., project staff use the partner's facilities for project activities);

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report

9. APPENDICES:

C›I›R›B

FOR THE NATIONAL CANCER INSTITUTE

CIRB Approval of Continuing Review

Date: March 1, 2022

Study ID: 10191

Study Title: A Phase 2 Study of M6620 (VX-970, berzosertib) in Combination with Carboplatin compared with Docetaxel in Combination with Carboplatin in Metastatic Castration-Resistant Prostate Cancer

Protocol Version Date: 05/04/21 Study Chair:

Atish Choudhury M.D.

On March 1, 2022, the NCI Adult CIRB - Early Phase Emphasis conducted its continuing review of 10191 and granted approval for 12 months minus 1 day. The continuing review of this study was conducted in accordance with the Federally-defined categories of expedited review stated in 45 CFR 46.110(b)(1)(i) and 21 CFR 56.110(b)(1) Category 8(a).

CIRB approval for this study will expire on February 28, 2023.

The following documents were reviewed:

1. CIRB Application (PVD 05/04/21)
2. Consent Form (PVD 05/04/21)
3. Protocol Version Date 05/04/21
4. Abstract ASCO 2021
5. ASCO Poster
6. Cumulative Inclusion Enrollment Report
7. DSMB Report dated January 2021
8. Investigator's Brochure for M6620 version 12 dated 11/23/21
9. Investigator's Brochure for M6620 Version 12 dated 11/23/21: Summary of Change
10. Toxicity Summary

Accrual to the study is closed. A copy of the current consent form (Protocol Version Date 05/04/21) is available on the CTSU website.

As the Study Chair, you are responsible for reporting all study-related activity and correspondence to the CIRB.

The CIRB complies with the Federal regulations 45 CFR 46, 21 CFR 50, and 21 CFR 56.

If you have any questions regarding this review, please contact the Adult CIRB - Early Phase Emphasis Coordinator at EarlyPhaseCIRB@emmes.com.

cc: Hannah Gallo, BS Austin Hill

Dana Farber ETCTN Office Matthew Bandel

Meredith Flynn

E01350.1a - Continuing Review Acknowledgement Memorandum (Proposal Number PC190196, Award Number W81XWH-20-1-0057)

Angela Urbina <angela.c.urbina.ctr@mail.mil>

Tue 1/4/2022 12:34 PM

To: Choudhury, Atish D.,M.D.,Ph.D. <ACHOUDHURY@PARTNERS.ORG>

Cc: Kimberly Odam <kimberly.l.odam.civ@mail.mil>; Andrea Kline <andrea.j.kline.civ@mail.mil>; Jodi Bennett <jodi.h.bennett.civ@mail.mil>; Angela Urbina <angela.c.urbina.ctr@mail.mil>; Nancy Englar <nancy.e.englar.civ@mail.mil>; Melanie Neagley <melanie.a.neagley.ctr@mail.mil>; Michelle Cromwell <michelle.l.cromwell.civ@mail.mil>

SUBJECT: Acknowledgement of the Continuing Review documents for the Protocol, "Molecular and Genetic Determinants of Response to Carboplatin With or Without an ATR Inhibitor (M6620) in mCRPC," Submitted by Dr. Atish Choudhury, MD, PhD, Dana-Farber Cancer Institute, in Support of the Proposal, "Molecular and Genetic Determinants of Response to Carboplatin with or without an ATR Inhibitor (M6620) in mCRPC," Submitted by Dr. Atish Choudhury, MD, PhD, Dana-Farber Cancer Institute, Boston, Massachusetts, Proposal Log Number PC190196, Award Number W81XWH-20-1- 0057, HRPO Log Number E01350.1a

1. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved the subject protocol on 15 January 2021.

2. The USAMRDC ORP HRPO received the Dana-Farber Cancer Institute Institutional Review Board (IRB) approval on 20 December 2021. The Dana-Farber Cancer Institute IRB approved continuation of the subject protocol on 15 December 2021; this approval will expire on 6 December 2022.

3. This correspondence serves to acknowledge HRPO receipt of the continuing review documents for the protocol. No further action related to this continuing review is needed. The documents in support of this continuing review will be placed in the HRPO file.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to usarmy.detrick.medcom-USAMRDC.other.hrpo@mail.mil. **Failure to comply could result in suspension of funding.**

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRDC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619- 2165), by email (usarmy.detrick.medcom-USAMRDC.other.hrpo@mail.mil), or by facsimile (301-619- 7803) or mail to the U.S. Army Medical Research and Development Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRDC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this study is Mrs. Angela Urbina, Human Subjects Protection Scientist, at 301-619-2370/angela.c.urbina.ctr@mail.mil.

Regards,

Mrs. Angela Urbina

Contractor - General Dynamics Health Solution
Administrative Support
Human Research Protection Office
USAMRDC Office of Research Protections (ORP)
Email: angela.c.urbina.ctr@mail.mil

Notification of IRB Outcome - Approval

Date: December 15, 2021

To: Atish Choudhury, MD
From: The Office for Human Research Studies (OHRS)

On 12/15/2021 the IRB reviewed the following protocol:

IRB Protocol Number:	20-661
Type of Review:	Submission Response for Continuing Review Form
Title:	Molecular and Genetic Determinants of Response to Carboplatin with or without an ATRInhibitor (M6620) in mCRPC
Principal Investigator:	Choudhury, Atish, MD
iRIS Reference Number:	420805
Review Process:	Expedite
Participating Sites:	Dana-Farber Cancer Institute (DFCI)

Current state of additional determinations (made previously or on this submission):

Risk Level:	Not Greater than Minimal Risk under 45 CFR 46 / 21 CFR 56
Expedited Review Category:	Category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)
Waiver of Consent:	Waiver/alteration approved 46.116(c) or (d)
HIPAA:	Waiver of HIPAA Authorization for Research approved under 45 CFR164.512 (i) (2) (ii)

The IRB approved the protocol from 12/15/2021 to 12/06/2022 inclusive. Within 60 days prior to the expiration date you must submit a continuing review or study completion and any required attachments. If continuing review approval or study completion is not granted before the expiration date, your protocol will be put on hold.

As Principal Investigator you are responsible for the following:

1. Submission in writing of any and all changes to this protocol (e.g., protocol, recruitment materials, consent form, study completion) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.
2. Submission in writing of any and all serious adverse event(s) that occur during the course of this protocol in accordance with the IRB's policy on adverse event reporting.
3. Submission in writing of any and all unanticipated problems involving risks to subjects or others.
4. Use of only IRB approved copies of the protocol, consent form(s), questionnaire(s), letter(s), and advertisement(s) in your research. Do not use expired consent forms.
5. Informing all investigators listed on the protocol of changes, adverse events, and unanticipated problems.

If you have any questions, please contact OHRS at OHRS@dfci.harvard.edu.

cc:
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