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• The author declares no potential conflicts of interest

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• Consultant for Bayer Healthcare Pharmaceuticals in 2017

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• My conflicts and Disclosures in the past 36 months are as follows (relevant or not relevant):

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Phase I Study of Niraparib in Combination with Radium-223 for the Treatment of Metastatic Castrate Resistant Prostate Cancer

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Abstract

PURPOSE: To identify the safety of niraparib, a PARP inhibitor, in combination with Radium-223 for the treatment of metastatic castrate resistant prostate cancer (mCRPC) in men without known *BRCA* mutations.

PATIENTS AND METHODS: Men with progressive mCPRC following ≥1 line of androgen receptor (AR)-targeted therapy and bone metastases but no documented *BRCA-1* or *BRCA-2* alterations or bulky visceral disease were included. Niraparib dose was escalated in combination with standard dosing of Radium-223 using a time-to-event continual reassessment method. The highest dose level with a DLT probability < 20% was defined as MTD. Secondary endpoints included PSA change and progression free survival. Exploratory analyses included assessing DNA mutations found in ctDNA as well as gene expression changes assessed in whole blood samples.

RESULTS: Thirty patients were treated with niraparib and radium-223: 13 patients received 100mg, 12 received 200mg and 5 patients received 300mg of niraparib. There were 6 DLT events: 2(13%) for neutropenia, 2(13%) for thrombocytopenia, while fatigue and nausea each occurred once (3%). Anemia (2/13%) and neutropenia (2/13%) were the most common grade 3 adverse events. For patients with prior chemotherapy exposure, the MTD was 100 mg, while the MTD for chemotherapy naïve patients was 200mg. Whole blood gene expression of PAX5 and CD19 were higher in responders and ARG-1, IL-2R and FLT3 expression were higher in non-responders.

CONCLUSIONS: Combining niraparib with Radium-223 in patients with mCRPC was safe however further studies incorporating biomarkers will better elucidate the role of combinations of PARP inhibitors with DNA damaging and other agents.

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Keywords

PARP; Niraparib; Radium-223; Castrate-Resistant; Prostate Cancer

INTRODUCTION:

An estimated 250,000 men were diagnosed with prostate cancer in 2021, which remains the second most common cause of cancer death for men in the United States (1). Prostate cancer cells are dependent on androgen stimulation and the androgen axis for growth and androgen deprivation therapy is the cornerstone of treatment (2). Despite androgen deprivation, progression of disease occurs over time, in part, through mechanisms that re-activate the androgen receptor (AR) independent of androgen stimulation, leading to castrate resistant prostate cancer (3). There are currently several different therapies for mCRPC that are approved which include: taxane chemotherapy, androgen axis inhibitors such has enzalutamide, apalutamide and abiraterone, sipuleucel-T, Radium-223 and in select populations, Poly (ADP-ribose) polymerase (PARP) inhibitors Olaparib or Rucaparib and Pembrolizumab, an anti-PD1 antibody (4–11).

Radium-223 is an alpha particle-emitting, radioactive agent that is FDA approved for treatment of patients with mCRPC and symptomatic bone metastases (12). In comparison to gamma radiation, alpha particle radiation produces higher rates of single strand DNA breaks that are more frequently converted to double strand breaks (13). The agent targets calcium hydroxyapatite in bone and accumulates in regions of osteoblastic activity, emitting alpha particles that have low penetrance depth and high linear energy transfer, making its effect localized to the cortical bone and minimizing bone marrow toxicity (14,15). This localized effect and minimal systemic toxicity creates the potential for Radium-223 to be combined safely with other agents.

Poly (ADP-ribose) polymerase 1 (PARP-1) is a nuclear enzyme that recruits proteins that impact the DNA damage repair (DDR) pathways. Inhibitors of PARP-1 have demonstrated clinical activity in mCRPC when concurrent mutations in genes that code for DNA repair proteins are identified (10,11,16). PARP may also play an important role in prostate cancer through interaction with the AR (17–20). Niraparib is an orally available, highly selective PARP-1/PARP-2 inhibitor that has shown activity in tumors with DNA repair deficiencies and is currently approved, at a dose of 200 to 300 mg daily, for clinical use in ovarian cancer (21–23). Niraparib has also been found to be effective in treating mCRPC with known DNA repair gene defects (24,25). The benefit of PARP inhibitors may also extend to patients with mCRPC without deficiencies in DDR pathways, as evidenced by the phase III results from the PROpel study, which demonstrated an improvement in PFS for patients without mutations in homologous recombination repair (HRR) genes (26).

We hypothesize that for patients with mCRPC, regardless of status of DNA repair mutational status, PARP inhibitors may prove effective when given in combination with agents that stimulate DNA damage. Given that Radium-223 creates high rates of DNA single strand breaks as a mechanism for cell death, and PARP is primarily responsible for repair of such breaks (27) there is the potential for synergy between these agents when treating

mCRPC. Additionally, the potential for niraparib to further suppress the AR pathway, suggests another potential mechanism for synergy when combined with Radium-223. We believe these interactions could extend benefit to patients without somatic or germline DNA repair mutations.

We conducted a phase IB study to determine the maximally tolerated dose (MTD) and recommended phase II dosing (RP2D) of niraparib combined with standard dosing of Radium-223 in the treatment of patients with metastatic mCRPC in men with and without prior chemotherapy exposure. Additional correlative studies were conducted to evaluate oncogenic genetic mutations at baseline and gene expression and pathway profile changes induced by therapy.

PATIENTS AND METHODS

Study Design and Participants

This was a multi-center, Phase IB dose escalation trial (ClinicalTrials.gov ID NCT03076203) that was approved by the institutional review boards at all participating institutions. Patients were provided written informed consent prior to starting on trial and enrollment followed international standards of good clinical practice. There were three dose levels of niraparib evaluated along with standard of care dosing of Radium-223 in two cohorts (chemotherapy naïve and prior chemotherapy) of men with mCRPC. The primary objective wacs to determine the MTD and RP2D of niraparib combined with Radium-223. The MTD was defined as the highest dose level at which the probability of a dose limiting toxicity (DLT) was less than 20%.

Since the toxicity of radium-223 is often delayed, a time-to-event continuous reassessment method (TITE-CRM) (28) design was used to identify the maximal tolerated dose (MTD) based on toxicities observed over 12 weeks of treatment (3 cycles of radium 223). A dose limiting toxicity (DLT) was defined as any treatment-related Grade ≥3 non-hematologic clinical that required medical intervention, or persisted for ≥7 days; any grade 4 hematologic toxicity with the exception of neutropenia Grade 4 lasting for <7 days and not associated with fever >38.5 degrees Celsius and/or infection; a dose interruption for a non-DLT laboratory abnormality lasting ≥14 days or a dose interruption for non-hematologic AE leading to <80% of an intended dose of niraparib being administered. Patients were followed from time of enrollment until progression of disease or death. The trial was conducted under the auspices of the Prostate Cancer Clinical Trials Consortium.

Eligible patients had histologic or cytologic diagnosis of adenocarcinoma of the prostate without neuroendocrine or small cell features, bone metastases detected by conventional bone scans and evidence of progressive disease after receiving at least 1 line of AR-targeted therapy in the hormone sensitive or castrate resistant setting. Each patient was required to have serum testosterone levels in the castrate range (less than 50 ng/dL) and this was measured at time of screening. Patients were ineligible if they had: previously received a PARP inhibitor, more than 1 prior line of AR-targeted therapy or more than one chemotherapy agent. Patients who were previously identified to be carriers of a pathogenic germline or somatic mutation in *BRCA-1* or *BRCA-2* were excluded; however, additional

testing to identify *BRCA* or other DDR pathway mutations was not conducted prior to enrollment. Additionally, patients with bulky visceral disease (defined as > 4cm), brain or leptomeningeal disease or impending spinal cord compression were excluded.

Treatment

Patients were assigned to one of the three different treatment arms based using TITE-CRM (28) design which allowed for three different dose levels of niraparib to be tested simultaneously with Radium-223. Subjects were given niraparib at doses of 100mg, 200mg or 300mg oral daily in combination with standard dosing of Radium-223, 55kBq per kg body weight, given at 4 week intervals for a total of 6 injections. Following 6 cycles, subjects were to continue on niraparib alone until objective progression, intolerance of therapy or withdrawal of consent. Enrollment was stratified by prior chemotherapy use and we aimed to enroll up to 30 patients total, with no more than 15 patients in each arm.

The TITE-CRM model was specifically chosen to improve the time to completion of the study, given that toxicities to Radium-223 are often delayed by several weeks. In the TITE-CRM, dose levels were assigned to each newly enrolled subject based on DLT data from subjects already enrolled on trial, which were weighted to account for the proportion of the observation period that each enrolled subject had been observed. Dose interruptions and reductions of niraparib were allowed for management of AEs per study protocol. The dose of radium-223 was not adjusted, both agents were held in the event of a DLT and radium-223 was not continued as a single agent in the event of niraparib discontinuation. Patients were removed from the study if they had an AE on the lowest dose of niraparib (100 mg) or if the subject required a dose interruption of more than 28 days. The study treatment also stopped for any patient who had clinical disease progression, intercurrent illness that made further treatment unsafe, developed myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), or withdrew of the consent.

Endpoints and Clinical Assessments

The primary outcome of this phase IB study was determination of the MTD and RP2D of niraparib combined with standard dosing of Radium-223 in the treatment of patients with mCRPC. Secondary endpoints included proportion of subjects with 50% prostate specific antigen (PSA) reduction at 12 weeks, radiographic progression free survival (rPFS) at 6 months and long-term safety and tolerability of treatment combination. AEs were defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Subjects were re-assessed for any AEs weekly for the first 4 weeks, then bi-weekly for the next 8 weeks and finally monthly until disease progression or death. Any individual who was withdrawn from the study due to an AE was followed until event had stabilized or resolved. Disease status (response or progression) was assessed every 12 weeks and were determined using a combination of the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria and the guideline for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group 3 (29,30).

Statistical Analysis

The TITE-CRM statistical design was used, assuming prior probabilities of toxicity for the three doses of 0.04, 0.08, and 0.12, with a target probability of toxicity for the optimal dose of 0.20, and a DLT evaluation time of 84 days. Calculation of the next dose to be assigned and the final toxicity probability estimates were performed using the SAS macro developed by the University of Michigan Comprehensive Cancer Center Biostatistics Unit (31). Patients were stratified within group by prior chemotherapy exposure and analyses were performed separately by strata. rPFS was estimated using the Kaplan-Meier method. Summary statistics were used to assess PSA change and to describe translational results. Time was calculated from day of first treatment until incidence of toxicity, progression or death.

Exploratory Correlative Endpoints

Gene expression changes in whole blood samples at baseline and during treatment (cycle 1, day 15 and cycle 3, day 15) were evaluated in 18 of 30 patients. RNA from whole blood, collected from participants, was isolated using the Qiagen miRNA isolation kit (32) and was analyzed using the PanCancer Immune Pathways and PanCancer Driver Pathways panels, as previously described (33). The PanCaner Driver and Immune Panels included 770 genes each from 24 different driver pathways and 13 cancer associated canonical pathways, respectively.

In addition, plasma samples were collected at baseline in 15 patients and analyzed for circulating tumor DNA (ctDNA) using the Guardant 360 Liquid Biopsy platform (34). Each sample was assessed for different somatic and germline mutations including single nucleotide variants (SNVs), insertions, deletions, gene fusions and copy number variants (CNVs). For the 15 other participants, there were not viable samples to run such analysis.

Data Availability Statement

Data from this study is available through the Prostate Cancer Clinical Trials Consortium by emailing PCCTC@mskcc.org.

RESULTS

Patients

From May 2018 to January 2020 30 patients were enrolled at 6 different clinical sites in the United States and patient demographics are included in Table 1. Two patients were withdrawn from the study early. One patient withdrew shortly after randomization and never received a dose of either trial medication. One patient in the prior chemotherapy cohort at dose level 2 (Niraparib 200 mg) was removed from the study due prolonged thrombocytopenia. The remainder of the patients continued therapy until progression of disease or death. All patients were included in treatment analysis. The median age of patients was 69 years. Twenty-five patients were Caucasian, five patients identified as black or African American. For patients who had previously received chemotherapy, the median time from completion of chemotherapy to treatment start date was 86 weeks (range 21 to 193 weeks).

Maximum Tolerated Dose

DLTs were evaluated in all three treatment groups and stratified by prior chemotherapy exposure (Table 2). There were no DLT events for patients who received the 100 mg dose of niraparib and no patients were removed from the study due to a treatment related adverse event. In the cohort that had never received chemotherapy, 7 patients received a 200 mg dose of niraparib and there was 1 DLT event, leading to an estimated probability of DLT at this dose level of 0.156 with a 95% confidence interval of 0.042 to 0.385. There were 2 DLT events in the 5 patients who received a 300 mg dose of niraparib, leading to an estimated probability of DLT for this cohort of 0.214. Since the probability of DLT was greater than 0.2 in the 300 mg cohort, the 200 mg dose of niraparib was confirmed as the MTD and RP2D in chemotherapy naïve patients. There were 3 DLT events in 5 patients who had previously received chemotherapy for the 200 mg treatment group, leading to an unacceptable DLT probability and a recommendation of 100 mg niraparib as the MTD and RP2D for patients with prior chemotherapy exposure.

Safety

There were 297 recorded adverse events that occurred during the trial, 153 of which were deemed attributable to study medications (Table 3). Most commonly, low grade disturbances to the gastrointestinal system occurred: with nausea (60%), diarrhea (30%) and constipation (27%) observed most frequently. Constitutional complaints such as fatigue (53%) and decreased appetite (27%) were also frequently observed. Significant hematologic toxicities were encountered infrequently, with only three patients with grade 3 or higher neutropenia. The average time to neutrophil recovery was 5.5 days, while the average time to platelet recovery was 18 days. There were no deaths considered related to study drug. One patient died secondary to widespread progression of disease and this event was not considered to be related to either study medication.

Clinical Outcome

PSA data was recorded for 28/30 patients. Of these, 9 patients had a PSA decline, of whom 3 had a PSA decline of > 50% (Supplemental Figure 1). For 5 participants, the PSA assessment was made prior to the 12^{th} week, given that progressive disease had already occurred.

The median rPFS for all patients included in analysis was 7.1 months (C.I. 2.7–9.3 months) with an estimated 6-month rPFS of 51% (C.I. 31–67%). For patients who were chemotherapy naïve (Figure 1A), the median rPFS was 2.9 months (C.I. 2.5–10.8 months) and for patients with prior chemotherapy exposure the median rPFS was 8.0 months (C.I. 2.7–10.3 months). The estimated 6 month rPFS for these groups was 47% (C.I. 21–69%) and 54% (C.I. 23–77%). Radiographic progression free survival distributions were similar by dose overall (Figure 1B) and in chemotherapy naïve (Figure 1C) and prior chemotherapy cohorts (Figure 1D).

Correlative Endpoints

We performed gene expression profiling in total RNA from blood obtained from patients at the stated time points, with the hypothesis that potential differences in gene expression

would be observed between patients experiencing longer duration on treatment as a surrogate marker for response. Indeed, several intriguing changes in gene expression profiles between patients based on treatment duration (median 21 weeks duration for the 18 patients that had viable RNA available for analysis) were detected. At baseline, paired box protein 5 (PAX5) and CD-19 expression were higher in the group that was on treatment for longer than 21 weeks in comparison to patients that stayed on treatment for less than 21 weeks (Figure 2A). By cycle 3 day 15, expression of both PAX5 (linear fold change = −5.08) and CD19 (linear fold change = −3.82) was more attenuated in the longer treatment duration group in comparison to the shorter treatment duration group.

In contrast, gene expression patterns for Interleukin-1 receptor type 2 (IL-1R2), Arginase 1 (ARG1), and FMS like tyrosine kinase 3 (FLT3) increased in the group treated for less than 21 weeks in comparison to the group treated for longer than 21 weeks (Figure 2B). Specifically, by cycle 3 day 15, ARG1 (linear fold change = 3.32), FLT3 (linear fold change = 3.32) and IL-1R2 (linear fold change = 2.80) had all markedly increased in patients who experienced a relatively faster time to progression. These changes in gene expression are intriguing and need further investigation in future studies.

ctDNA was detected in 14/15 samples collected at baseline. Of these, 7 had *AR* amplification and 4 instances of point mutations within the gene were detected (Table 4). Somatic mutations in *TP53* and *PIK3CA* were detected in 7 and 4 patients respectively as well. Deletions in *RB1* and *BRCA2* were also detected via copy number variations in 7 and 4 patients respectively. There were 6 mutations found in *BRCA2*, two of which were germline SNVs, and one mutation found in *ATM* and *CDK12 genes*, respectively. Notably, the median time to progression for 7 patients with HRR variants was only 21 weeks; however, the median time to progression for the two patients with germline *BRCA2* mutations was 43 weeks, significantly longer than the median duration for the entire population.

DISCUSSION:

This multi-center phase IB trial was the first to assess the combination of a PARP inhibitor with Radium-223 in patients with mCRPC without known *BRCA* mutations. The combination of 200 mg of niraparib with standard dosing of radium-223 was found to be tolerable in a subset of patients who were chemotherapy naïve, while a dose of 100 mg niraparib was tolerable for patients who had experienced prior treatment with taxane therapy. Currently, the combination of olaparib with radium-223 is under investigation and investigators used a 3+3 trial design to evaluate 12 patients at two different dose levels of olaparib, determining 200 mg twice daily as their R2PD (35). Importantly, our study demonstrates the feasibility and utility of the TITE-CRM statistical design when investigating therapeutics that have a delayed toxicity profile like radio-ligands. We were able to safely evaluate 30 patients over three different dose levels simultaneously, which accelerated trial accrual without exposing participants to excess risk. This trial can serve as a framework for the development of other combined modality therapies using radio-ligands, which may prove pivotal with the recent approval of Lu 177 vipivotide tetraxetan for patients with mCRPC (36).

By down regulating several DNA repair pathways, PARP inhibitors have gained interest as radiosensitizers in many different cancer models and recent studies have demonstrated safety of PARP inhibitors with other radiation modalities (37–39). Our study adds to these findings as we were able to show tolerability of 200 mg of niraparib with standard of care dosing of Radium-223 in patients without prior chemotherapy exposure. The majority of adverse events related to therapy were either grade 1 or 2, with nausea, diarrhea or constipation and fatigue reported as the most common symptoms. Despite potential overlapping toxicities to the bone marrow, we did not observe significant issues with impaired hematopoiesis and there were few grade 3 events of cytopenia. In all but 1 instance, the cytopenia resolved after holding niraparib. There were no instances of grade 3 infections and there were no deaths attributable to study medications.

Currently niraparib is approved as a monotherapy for treatment of ovarian cancer at 300 mg daily and studies are ongoing in biomarker selected metastatic prostate cancer patients at 200 mg daily in combination with abiraterone acetate 1000 mg. In regards to combination with radiation therapy, studies evaluating Olaparib in lung and glioblastoma have concluded that, when combined with radiation, the MTD of Olaparib needs to be reduced from the recommend monotherapy dose in order to limit hematologic toxicity (37,40). Additionally trials are currently enrolling that are testing reduced doses, 100 mg or 200 mg, of Niraparib in combination with radiation therapy for high risk early stage prostate cancer (41,42). Recently de Haan and colleagues were able to show that a 25 mg dose of Olaparib was able to effectively reduce baseline poly ADP-ribose (PAR) levels along with radiation induced PARylation in lung tumor tissue and peripheral blood mononuclear cells, concluding that a reduced dose of a PARP inhibitor still has biologic activity in combination with radiation therapy (37). Taken together, our findings that using either 100 mg or 200 mg doses of Niraparib in combination with radiation therapy are not likely to drastically reduce the clinical activity of the PARP inhibitor.

Our translational studies demonstrate that using the NanoString platform to perform gene expression profiling on whole blood samples was feasible. Although one limitation to testing whole blood is the uncertainty of the source of RNA, whether it is tumor-derived vs. from normal cells (43).

We observed differences in PAX5 and CD19 expression when comparing patients who had a response to therapy to those without a response. At baseline, RNA transcripts were higher for both of these targets in responders compared to non-responders and a statistically significant reduction in mRNA level was observed with treatment in those who remained on study for longer than 21 weeks. PAX5 is an oncogene that encodes a potent transcription factor leading to B-cell development and aberrant expression has been observed frequently with development of aggressive B-cell malignancies (44). CD19, a cell surface marker expressed on all B lymphocytes, is critical for cell function and CD19 expression is in part regulated by PAX5 (45). Additionally, significant PAX5 expression has also been demonstrated in non-lymphoid malignancies, including breast, small cell lung cancer and pediatric tumors and is believed to play a role in cell survival and metastatic potential (44). One down-stream target of PAX5 is c-MET, a tyrosine kinase receptor for which mutations and aberrant expression are known promote oncogenesis (46).

B-cells in the tumor microenvironment can promote tumorigenesis and increase metastatic potential by causing antibody mediated T-cell suppression, promoting lymphangiogenesis and producing immunomodulatory cytokines that suppress the anti-tumor immune response (47). In prostate cancer, it has been observed that B-cell infiltration is higher in high grade tumors and in tumors that eventually recurred or progressed in comparison to low or intermediate grade tumors (48). Additionally, infiltrating B cells were shown to support castrate resistant cell growth by secreting lymphotoxin which lead to cell survival (49).

ARG1 expression was similar at baseline when comparing patients who responded to therapy to those who did not; however, in the patients who did not respond to therapy, by cycle 3 day 15, *ARG1* expression was nearly 4 times higher. This suggests that expression of *ARG1* could possibly serve as a protective mechanism, limiting the effect of treatment. *ARG1* expression by tumor associated macrophages (TAMs) has been demonstrated as a mechanism to suppress the effect of infiltrating T cells by limiting the amount of L-arginine available for T cell function (50). Interestingly we observed expansion of *FLT3* transcripts mirrored *ARG1* in patients who had relatively faster time to progression. *FLT3* critically drives dendritic cell maturation and activity in the tumor microenvironment. This may either lead to an amplified immune response, through increased antigen presentation to infiltrating cytotoxic T cells, or diminished local immune response, by expansion of T regulatory cells (Treg) (51).

With these hypothesis-generating observations in whole blood RNA expression, a speculative mechanism for the effect of niraparib with Radium-223 may be through the immune response within the tumor microenvironment. In patients who stayed on treatment for longer than 21 weeks we observed changes indicative of decreased B-cell function which may allow for increased immune activity within the microenvironment. Conversely, resistance to therapy may be mediated through decreased local T-cell activity, by increased ARG1 expression by TAMs and *FLT3* expression driving Treg expansion. Further investigation is needed to explore this phenomenon, but if the mechanism is valid, one could speculate that adding therapies to improve T-cell mediated immune response could augment this therapeutic approach. Notably, recent phase III trials have reported improved outcomes in mCRPC when combining PARP inhibitors with abiraterone acetate plus prednisone in those with germline/somatic homologous recombination defects, with potentially a less robust benefit in unselected patients (25,52). Trials are also evaluating the combination of PARP inhibitors with other androgen inhibitors, immune checkpoint inhibitors and Lu-PSMA-617 (53–55). Thus, the optimal combination partner remains to be determined.

Our exploratory analysis of baseline ctDNA discovered 4 patients with somatic *BRCA* variants and two patients that had germline *BRCA2* mutations. These two patients were in the 300 mg and 100 mg cohorts and had dramatically longer times to progression of 38 and 49 weeks, respectively. Additionally, the patient in the 100 mg cohort had previously received chemotherapy. These outcomes are concordant with prior observations of favorable responses to Radium-223 in patients with known *BRCA* mutations (56–58), in addition to the apparent effect of PARP inhibitors in this population. Given the known efficacy of PARP inhibitors in patients with germline/somatic BRCA mutations, we intentionally excluded

patients with prior record of these alterations at trial enrollment. However, this expected finding highlights the impact of ctDNA analysis and further demonstrates the importance of screening patients for molecular biomarkers before choosing therapies.

This study was not powered nor designed to evaluated efficacy, but we were able to collect data on PSA change and rPFS to help describe trends. PSA increased in the majority of patients on study; however, rapid PSA response is not a hallmark of Radium-223 therapy, as Radium-223 can cause an early PSA flare in patients who are responding to therapy (59,60). Nearly 30% of patients had a PSA decline, however only 10% had a PSA decline of > 50% at week 12. Three of the 9 patients with a PSA decline were found to have *BRCA* mutations on ctDNA; 5 of the remaining 6 patients did not have blood samples evaluated for ctDNA. In regards to rPFS, there did not appear to be a statistically significant difference between patients who had prior chemotherapy exposure and those who were chemotherapy naïve, with wide overlapping confidence intervals ranging from 2.5 to 10.8 months.

In conclusion, niraparib in combination with Radium-223 was demonstrated to be safe in combination for the treatment of mCRPC for patients who have previously progressed on AR therapies. We intend to continue investigation with a prospective phase II trial that will better evaluate efficacy endpoints and assess potential long term toxicities and will serve as a companion to the ongoing trial of olaparib with Radium223 in unselected patients with mCRPC (35).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TRANSLATIONAL RELEVANCE:

Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated to be effective in treating mCRPC that harbor mutations in DNA damage repair (DDR) pathways. However, their effectiveness outside this population is limited and investigation into their role in combination with other therapies is prudent. Additionally, advances in radiopharmaceuticals in metastatic castrate resistant prostate cancer (mCRPC) has created a need for trials evaluating their safety with other approved agents. This novel designed Phase 1b study evaluated the safety and tolerability of niraparib combined with Radium-223 in treatment of men with mCRPC. We were able to demonstrate the utility of a time-to-event continuous reassessment method of enrollment and the combination of therapies proved to be manageable with a 200 mg dose of niraparib. While the combination was safe no increase in clinical activity was found. We demonstrated that gene expression profiling on whole blood was feasible and observed different patterns in expression of immunomodulatory genes between responders and non-responders to therapy.

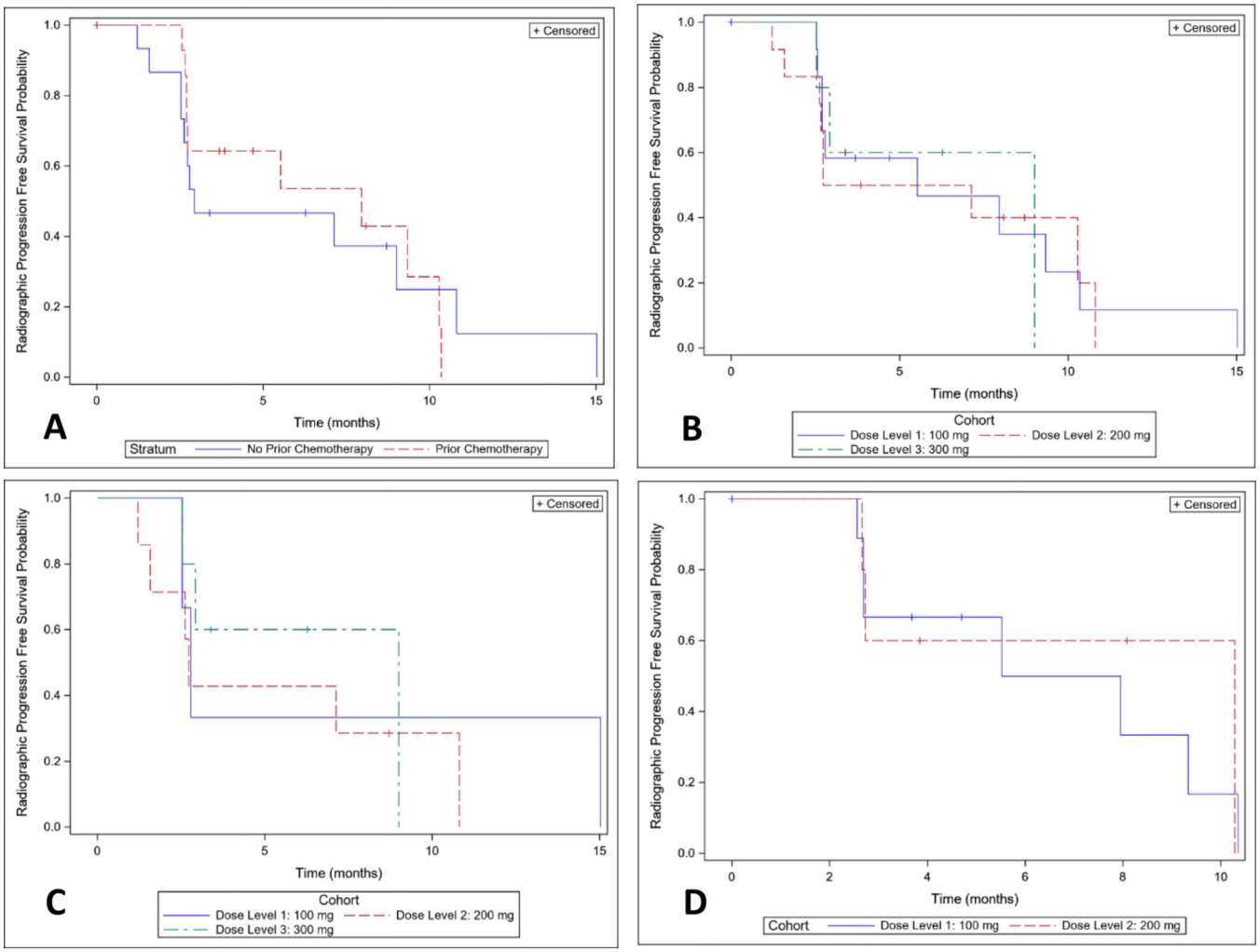

Figure 1: Radiographic Progression Free Survival (rPFS):

A) Overall rPFS stratified by prior chemotherapy exposure; **B)** Overall rPFS stratified by dose cohort; **C)** rPFS of the chemotherapy naive cohort, stratified by dose cohort; **D)** rPFS of the prior chemotherapy exposed cohort stratified by dose cohort.

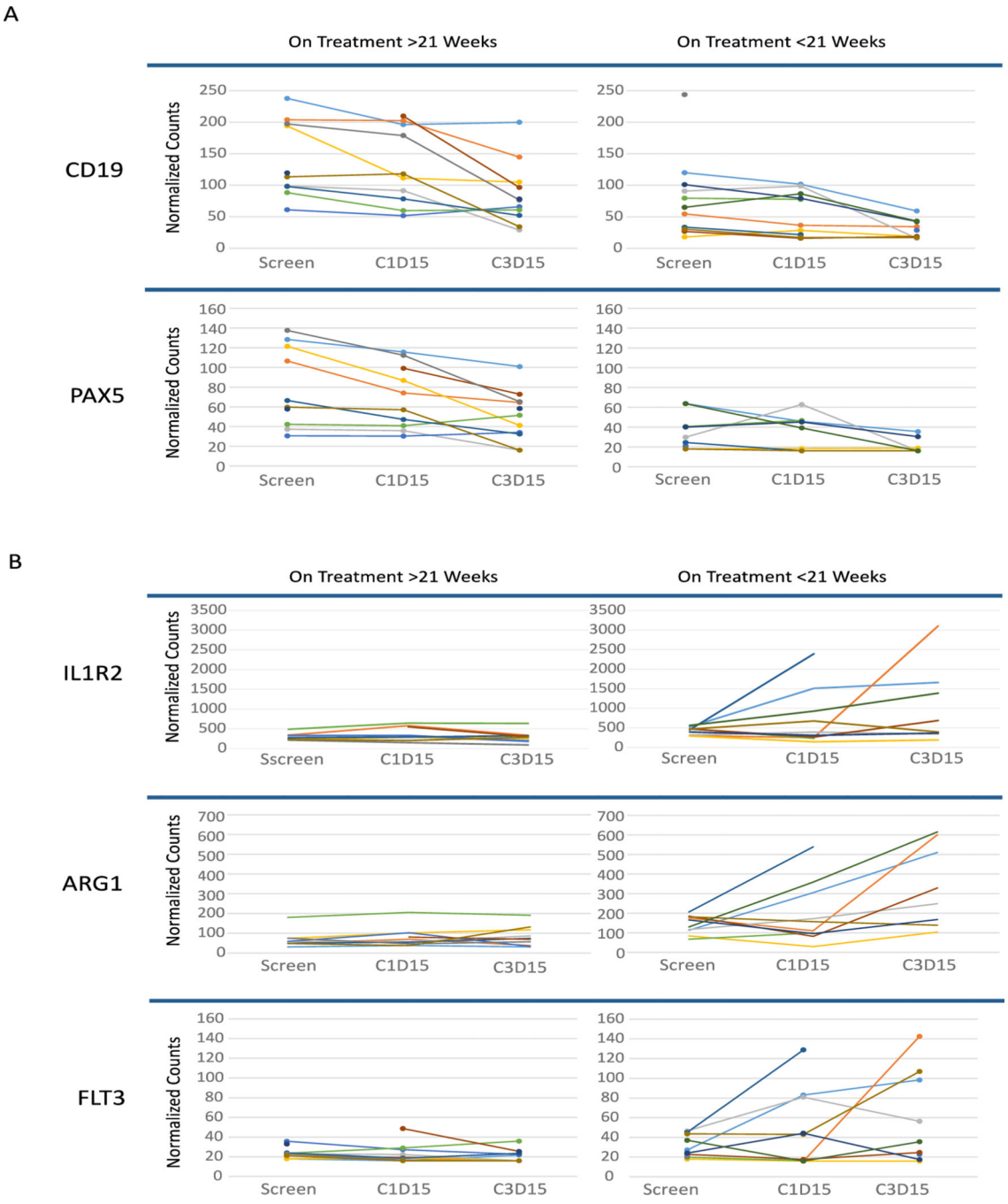

Figure 2. Gene expression differences in blood from enrolled patients with treatment duration greater or less than median 21 weeks.

A) CD19 and PAX5 expression appears to be higher at baseline and decrease with treatment in patients treated longer than median 21 weeks compared to patients treated less than 21 weeks. **B)** IL1R2, ARG1, and FLT3 expression increases over time in patients with duration of treatment shorter than median 21 weeks but does not in patients with treatment of duration than median 21 weeks.

Table 1:

Patient, Tumor and Treatment Characteristics

Study Arm	100mg (N=13)	200mg (N=12)	300mg (N=5)
Patient Characteristics			
Age (median, years)	71	66	73
ECOG Performance status 0 1	 6 (46%) 7 (54%)	 8 (67%) 4 (33%)	 3 (60%) 2 (40%)
Race Caucasian African American	 11 (85%) 2 (15%)	 10 (83%) 2 (17%)	 4 (80%) 1 (20%)
Baseline Hemoglobin (median, g/dL)	11.7	12.4	13.1
Baseline Platelet Count (median, B/L)	212	217	244
Disease Characteristics			
Total Gleason Score at Diagnosis 6 7 8–10	 0 3 (23%) 10 (76.9%)	 3 (25%) 1 (8.3%) 8 (66.7%)	 1 (20%) 1 (20%) 3 (60%)
Sites of Metastases Bone Only Bone and Lymph Node Only Visceral Metastases	 6 (46%) 3 (23%) 2 (15%)	 6 (50%) 3 (25%) 2 (16%)	 2 (40%) 3 (60%) 0
Treatment Characteristics			
Prior Prostatectomy	1 (8%)	2 (17%)	2 (40%)
Prior Definitive Radiation Therapy	5 (38%)	3 (25%)	1 (20%)
Prior AR Signaling Inhibitors Abiraterone Enzalutamide	 7 (54%) 6 (46%)	 8 (67%) 4 (33%)	 2 (40%) 2 (40%)
Prior Chemotherapy Docetaxel Cabazitaxel	10 (77%) 9 (69%) 1 (8%)	5 (42%) 5 (42%) 0	0 0 0

Table 2:

Probabilities of Dose Limiting Toxicities

Chemotherapy Naïve			
Dose Level	**Patients Treated**	**DLTs**	**DLT Probability**
100 mg	3	0	0.089 (0.019 – 0.281)
200 mg	7	1	0.156 (0.042 – 0.385)
300 mg	5	2	0.214 (0.068 – 0.455)

Prior Chemotherapy Exposure			
Dose	**Patients Treated**	**DLTS**	**DLT Probability**
100 mg	10	0	0.127 (0.029 – 0.352)
200 mg	5	3	0.207 (0.061 – 0.455)
300mg	0	0	0.272 (0.095 – 0.521)

Table 3:

Most Frequently Observed Treatment Related Adverse Events

	Prior Chemotherapy Exposure		Chemotherapy Naïve		
Dose Level	**100mg**	**200mg**	**100mg**	**200mg**	**300mg**
Patients	**10**	**5**	**3**	**7**	**5**
Max Grade 2 TRAE					
Hematologic					
Anemia	1 (10%)	1 (20%)	-	1 (14%)	1 (20%)
Thrombocytopenia	2 (20%)	1 (20%)	-	2 (29%)	-
Neutropenia	2 (20%)	1 (20%)	-	-	-
Gastrointestinal					
Diarrhea	2 (20%)	1 (20%)	-	3 (43%)	3 (60%)
Constipation	3 (30%)	-	-	2 (29%)	3 (60%)
Dry Mouth	1 (10%)	-	-	2 (29%)	1 (20%)
Nausea	4 (40%)	4 (80%)	1 (33%)	5 (71%)	3 (60%)
Vomiting	-	1 (20%)		2 (29%)	1 (20%)
Other					
Hypertension	2 (20%)	-	1 (33%)	-	-
Fatigue	4 (40%)	3 (60%)	-	3 (43%)	5 (100%)
Decrease Appetite	3 (30%)	1 (20%)	2 (67%)	2 (29%)	-
Max Grade 4 TRAE					
Hematologic					
Anemia	-	1 (20%)	-	1 (14%)	1 (20%)
Thrombocytopenia	-	1 (20%)	-	1 (14%)	-
Neutropenia	-	2 (40%)	-	-	1 (20%)
Gastrointestinal					
Nausea	-	-	-	-	1 (20%)
Other					
Hypertension	1 (10%)	1 (20%)	1 (33%)	-	1 (20%)

Table 4:

Baseline ctDNA results for samples with Relevant Co-occurring Alterations

Patient Number	SNV/InDel	CNV	Dose and Cohort	Time to Progression (weeks)
1	CDK12 K480 CDK12 L867P AR L702H		100 mg - C	19
2		AR amplification RB1 homozygous del	200 mg - C	30
3	PIK3CA N345K ATM M2405V AR L702H	BRCA2 LOH deletion RB1 deletion AR amplification	200 mg - N	13
4		AR amplification BRCA2 homozygous del RB1 LOH deletion	200 mg - N	31
5	PIK3CA N345K	PIK3CA amplification AR amplification RB1 homozygous del	100 mg - N	15
6	AR W742C EGFR D837N	RB1 homozygous del EGFR amplification	100 mg - N	32
7	AR F877L PIK3CA H1047R	ATM LOH deletion BRCA2 LOH deletion RB1 deletion	100 mg - N	21
8	BRAF K601E AR T878A BRCA2 H1003fs (g) BRCA2 Q2859fs RB1 L572fs		300 mg - N	38
9		BRCA2 deletion RB1 LOH deletion PIK3CA amplification AR amplification	200 mg - C	12
10	BRCA2 c682–1G>A BRCA2 K2849fs (g)		100 mg - C	49
11	PIK3CA H1047R	AR amplification	100 mg - C	18

Legend: ctDNA = circulating tumor DNA, C = prior chemotherapy, N = chemotherapy naïve, CNV=copy number variant, SNV= single nucleotide variant, InDel= insertion/deletion variant, LOH = loss of heterozygosity, del = deletion, fs = frameshift, (g) = germline