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A Phase I Study of Combination Olaparib and Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Bone Metastases (COMRADE)

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Abstract

Given that radium-223 is a radiopharmaceutical that induces DNA damage, and olaparib is a PARP inhibitor that interferes with DNA repair mechanisms, we hypothesized their synergy in metastatic castration-resistant prostate cancer (mCRPC). We sought to demonstrate the safety and efficacy of olaparib + radium-223.

We conducted a multicenter phase I 3+3 dose escalation study of olaparib with fixed dose radium-223 in patients with mCRPC with bone metastases. The primary objective was to establish the RP2D of olaparib, with secondary objectives of safety, PSA response, alkaline phosphatase response, radiographic progression-free survival (rPFS), overall survival, and efficacy by homologous recombination repair (HRR) gene status.

Twelve patients were enrolled; all patients received a prior androgen receptor signaling inhibitor (ARSI; 100%) and 3 patients (25%) prior docetaxel. Dose-limiting toxicities (DLT) included cytopenias, fatigue, and nausea. No DLTs were seen in the observation period however delayed toxicities guided the RP2D. The RP2D of olaparib was 200 mg orally twice daily with radium-223. The most common treatment-related adverse events were fatigue (92%) and anemia (58%). The rPFS at 6 months was 58% (95% confidence interval, 27%–80%). Nine patients were evaluable for HRR gene status; 1 had a BRCA2 alteration (rPFS 11.8 months) and 1 had a CDK12 alteration (rPFS 3.1 months).

Olaparib can be safely combined with radium-223 at the RP2D 200 mg orally twice daily with fixed dose radium-223. Early clinical benefit was observed and will be investigated in a phase II study.

Introduction

Prostate cancer is the most common solid organ malignancy in men and is the third leading cause of cancer death in men, a large portion of which are attributed to the emergence of metastatic castration-resistant prostate cancer (mCRPC; ref. 1). Prostate cancer most commonly metastasizes to the bone and many patients develop bone-only metastases, a significant source of morbidity and mortality. The pathogenesis of bone metastasis involves bone remodeling that releases growth factors that stimulate prostate cancer cell proliferation.

This causes a cycle of bone breakdown, tumor growth, and osteoblastic metastasis formation (2). More effective strategies to target bone metastases in prostate cancer are warranted.

Radiopharmaceuticals have emerged as a treatment strategy for patients with mCRPC. Radium-223 is an alpha-emitting radioisotope that acts as a calcium-mimetic with natural bone-seeking proclivity, and induces cytotoxic DNA double-strand breaks (DSB; ref. 3). This radiopharmaceutical has particular benefit in outcomes of patients whose prostate cancer harbors mutations in homologous combination deficiency genes such as *ATM*, *BRCA2*, and *CDK12* (4). The efficacy of radium-223 in mCRPC was demonstrated in the international phase III ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial (5). The study enrolled patients with mCRPC and symptomatic bone metastases to receive radium-223 or matching placebo. The trial demonstrated that radium-223 improved overall survival (OS) compared with standard of care [14.9 vs. 11.3 months; HR, 0.70; 95% confidence interval (CI), 0.58–0.83; $P < 0.001$] and was a landmark study as the first study of any radiopharmaceutical to demonstrate an OS benefit.

A common characteristic of radiation used in the clinical treatment of cancer is the induction of various types of DNA damage, including single-strand breaks (SSB) and DSB directly leading to tumor cell death (6). A key determinant of cell survival following radiation is the ability of tumor cells to repair DNA damage through efficient repair mechanisms, including PARP, which is necessary for base excision repair of SSB. Olaparib inhibits various isoforms of PARP (PARP-1, -2, -3), and has been shown to decrease *in vitro* and *in vivo* tumor growth in models of human cancer (7). In May 2020, Olaparib was FDA-approved in a selected population of men with mCRPC with homologous recombination repair (HRR) gene alterations based on results from the PROfound trial. This trial demonstrated that in men with mCRPC, olaparib had improved progression-free survival (PFS) compared with enzalutamide or abiraterone (7.4 vs. 3.6 months; 95% CI, 0.25–0.47; $P < 0.001$; ref. 8).

By combining radiation with PARPi, the SSB induced by radiation go unrepaired by PARP-associated base-excision repair, leading to cell death and tumor growth delay (9). *In vitro* and *in vivo* studies in several different cancer models have confirmed the synergistic effects of PARPi and radiation therapy (10). Lui and colleagues demonstrated the ability of the PARPi veliparib to radiosensitize human prostate cancer cells under euoxic and hypoxic conditions (10). In addition, Schiewer and colleagues demonstrated similar effects with veliparib in both hormone sensitive and CRPC cells exposed to genotoxic insult with ionizing radiation and docetaxel in a dose-dependent manner (11). Preclinical and clinical studies across other solid tumors including those of the head and neck, colon, lung, and glioblastoma have demonstrated radiosensitizing effects of PARPi with radiation (12-17). These data highlight the role of PARPis as radiosensitizing agents and provide rationale for combining olaparib with radium-223 in men with mCRPC. The combination of radium-223 with olaparib may demonstrate antitumor activity in patients with mCRPC irrespective of underlying HRR deficiency status. This phase I/II study seeks to determine the RP2D of olaparib in combination with radium-223, as well as evaluate safety and tolerability, early efficacy, and biomarkers of response.

Materials and Methods

Patients

Eligible patients had histologically or cytologically confirmed prostate cancer with progressive castration-resistant disease as defined by PCWG3 criteria (18). Patients were required to have ≥2 bone metastases by radiographic imaging, at least one lesion which had not been treated with prior radiation therapy, no visceral metastases, and lymphadenopathy less than 4 cm in short diameter. Patients could have received any amount of prior therapy for mCRPC but could not have received prior PARPi or radium-223. All patients were treated with a bisphosphonate or denosumab unless medically contraindicated. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 1. The Institutional Review Board at each participating center approved the study, which was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. All patients were provided written informed consent.

Study design and treatment

This was an open-label, phase I/II study evaluating the dosing, safety, and efficacy of olaparib in combination with radium-223 in men with CRPC with bone metastases (NCT03317392). The study was conducted at nine US institutions in the Experimental Therapeutic Clinical Trials Network (ETCTN) of the NCI.

A standard 3+3 dose escalation design was employed with fixed dosing of radium-223 (55 kBq/kg or 1.49 microcurie/kg) administered as a bolus intravenous injection at intervals of every cycle (1 cycle = 28 days) for up to 6 cycles (± 7 days) and four planned dose levels for olaparib. The starting dose of olaparib was 200 mg orally twice daily (dose level 1 or DL1) continuously with one dose escalation to 300 mg orally twice daily (dose level 2 or DL2) continuously and two-dose de-escalation to 150 mg (dose level −1) and 100 mg (dose level −2) orally twice daily continuously. All trial treatment continued until disease progression or unacceptable toxic effects, with olaparib continuing beyond the fixed 6 cycles of radium-223. Dose reductions were not allowed for radium-223 but were permitted for olaparib, according to the protocol. Dose delays for adverse events (AE) were permitted for olaparib and radium-223. Dose-limiting toxicities (DLT) were based on toxicities graded using the Common Terminology Criteria for Adverse Events (CTCAE) scale (version 5.0), and include the following:

- Grade 4 neutropenia lasting >7 days.
- Grade 3 or 4 neutropenia with fever >38.5°C.
- Grade 4 thrombocytopenia, or grade 3 thrombocytopenia with active bleeding.
- Grade 4 anemia.
- Grade 3 electrolyte or biochemical disturbances considered related to drug therapy that cannot be treated and recover to ≤grade 2 within 48 hours.

- Grade 3 or 4 non-hematologic toxicity considered related to drug therapy. Only includes diarrhea, nausea or vomiting when optimal prophylactic measures have been prescribed.

The DLT evaluation period was the first two cycles. The dose of olaparib could be modified, while the dose of radium-223 could be delayed but not modified. Herein, we report the results of the phase I study. The phase II portion randomizes patients to receive either olaparib plus radium-223 or radium-223 alone and is currently ongoing.

Study endpoints

The primary objective of the phase I study was to determine the RP2D of olaparib in combination with fixed dosing of radium-223 in men with mCRPC. The secondary objectives included PSA response >50% decline from baseline (PSA_{50}) defined by PCWG3 criteria (19), alkaline phosphatase response (>30% decline from baseline) defined based on the ALSYMPCA study (5), investigator-assessed objective response rate defined by RECIST version 1.1[19] for patients with measurable lymph node metastases, investigator-assessed radiographic progression-free survival (rPFS), and OS. rPFS was defined as the time from enrollment to radiographic progression, by PCWG3 criteria for bone metastases or RECIST version 1.1 for soft-tissue metastases, or death from any cause, whichever came first censored at the date of last disease assessment. OS was defined as the time from enrollment to death of any cause, censored at the date of last follow-up.

Assessments

All eligible patients underwent a baseline biopsy of either a bone or lymph node metastasis prior to initiation of therapy. In addition, archival tissue was collected when available. Safety was assessed by monitoring AEs, graded according to the CTCAE version 5.0. Physical exam, vital signs and ECOG performance status were assessed on Day 1 of each 4-week cycle. Laboratory assessments were done up to 7 days prior to Day 1 and Day 15 for cycles 1 and 2, and up to 7 days prior to Day 1 for all subsequent cycles. Imaging assessments including CT chest, CT/MRI abdomen and pelvis and technetium-99 m bone scan occurred every at baseline, and every 12 weeks until radiographic disease progression.

Biomarker studies

Biomarker studies were prospectively planned. Studies on tumor tissue included the OncoPanel assay, a CLIA-certified, next-generation sequencing (NGS) test that examines over 400 genomic loci for single nucleotide variants, including >100 DNA repair genes, small insertions or deletions, and copy-number variants (20). In addition, RAD51 was evaluated by IHC. This assay can identify RAD51-foci in cryo-sections or sections of formalin-fixed, paraffin embedded tumor biopsies. The presence of RAD51 sub-nuclear foci is a surrogate functional measure of homologous recombination (HR) proficiency of the tumor sample, and its presence or absence with somatic and germline HR gene mutation status was evaluated (21). Criteria for interpretation of tissue staining is listed in the Supplementary Appendix.

Statistical analysis

Patient and disease characteristics were summarized descriptively as median and range for a continuous variable and frequency for a categorical variable. Time to event endpoints (rPFS and OS) were estimated using the method of Kaplan–Meier with 95% CIs. A swimmer plot displayed treatment dose and duration (Fig. 1). A waterfall plot portrayed the maximum decline in PSA or alkaline phosphatase from baseline (Fig. 2). For toxicity reporting, DLT and treatment-related adverse event (TRAE) were reported separately for each dose level evaluated. HRR gene mutation status was listed as case reporting given the exploratory nature and small number of patients. Statistical analysis was performed with SAS 9.4 software (SAS Institute, Cary, NC).

Data availability statement

The data generated in this study are available within the article and its Supplementary Data files.

Results

Patient population

A total of 12 patients were enrolled on the phase I study between February 2019 through August 2020. Baseline patient characteristics are summarized in Table 1. All patients (100%) had prior androgen receptor signaling inhibitor (ARSI). Three (25%) patients received prior docetaxel. Ten patients were on concurrent osteoclast targeting agent, all of whom received denosumab.

Treatment exposure

The median number of olaparib cycles received was 3 (range 3–26) at DL1 and 6.5 (range 3–13) at DL2, with the median number of radium-223 cycles received being 3.5 (range 3–6) at DL1 and 6 (range 3–6) at DL2. At the time of data cutoff, one patient treated at DL1 was still on therapy, eight patients had discontinued treatment due to disease progression, and 3 patients had discontinued treatment due to AEs or intolerable toxicities. The treatment summary is detailed in a swimmer plot (Fig. 1).

Safety and toxicity

Three patients (#1–3) were initially allocated to olaparib at DL1 (trial schema and dose escalation scheme in Supplementary Appendix Figure S1 and Supplementary Table S1). There were no DLTs observed and therefore the study proceeded to DL2. Initially, 3 patients were enrolled on DL2. When no DLTs were observed, the study enrolled an additional three patients to DL2 with no DLTs observed. However, we observed that 5 of the 6 patients enrolled at DL2 experienced AEs outside of the DLT window. Patient #4 required a dose reduction at the start of cycle 7 for grade 2 nausea, patient #5 at the start of cycle 4 for grade 2 neutropenia, patient #6 at the start of cycle 3 for grade 2 fatigue and grade 2 nausea, patient #7 at the start of cycle 3 for grade 3 anemia, and patient #8 at the start of cycle 3 for grade 2 neutropenia. After review by the study safety committee comprised of all the study principal investigators, site principal investigators, and study nurse practitioner;

the decision was made that DL2 (300 mg orally twice daily) was not well tolerated. All treatment-related grade ≥3 toxicities were reviewed at monthly meetings, through Theradex Web Reporting monthly reviews, and also through safety analyses from the statistical team. It was recognized that increased grade 3–4 toxicity was observed just outside of the DLTs monitoring period. This information was discussed with the safety committee and the decision was made to proceed with lower olaparib dosing. Another 3 patients (#10–12) were then enrolled at DL1 for a total of 6 patients at that dose level. No DLTs were observed at DL1 and the RP2D was deemed to be 200 mg orally twice daily.

A summary of TRAEs is provided in Table 2. All twelve (100%) patients had any grade TRAEs. Five of 12 patients (42%) had grade 3–4 TRAEs: at DL1, 2 patients experienced grade 3 anemia (neither of whom received prior docetaxel), and 1 patient who received prior docetaxel developed grade 3 thrombocytopenia. At DL2, 1 patient had grade 3 anemia and grade 4 lymphopenia, and 1 patient had a grade 3 stroke; these patients had not received prior chemotherapy. There were no grade 5 events. A summary of all AEs regardless of attribution (treatment-related or unrelated) is in Supplementary Table S2, and Supplementary Table S3 lists all grade 3 or higher AEs and treatment cycles at AE occurrence.

Treatment outcomes

Overall, 2 of the 12 patients (16.7%) had a confirmed PSA response: one patient receiving olaparib at DL1 and 1 patient receiving olaparib at DL2 (Table 3; Supplementary Fig. S2). A waterfall plot of PSA response is shown in Fig. 2A. The majority of patients experienced an alkaline phosphatase response, with 3 patients (50%) at DL1 and 5 patients (83.3%) at DL2 (Table 4, Fig. 2B). For the entire cohort, the rPFS at 6 months was 58% (95% CI, 27%–80%), with a 12-month OS of 56% (95% CI, 24%–79%); Kaplan–Meier survival curves are illustrated in Fig. 2C and D.

HRR gene status

Samples from tumor biopsies performed prior to treatment were available for 9 of 12 patients. OncoPanel testing on biopsy specimens revealed that 2 of 9 patients had tumors with aberrations in HRR genes: *CDK12* (rPFS 3.1 months) and *BRCA2* (rPFS 11.8 months). There were four specimens available for additional RAD51 IHC staining to assess functional HRR: these samples were stained for geminin, a cell cycle S-phase marker that is informative for the RAD51 assay due to HR being restricted to the S-phase. Two samples were geminin positive (>3% of geminin positive cells) and therefore evaluable for RAD51. Among the two geminin-positive samples, one had no evidence of RAD51-foci positive nuclei (HR-deficient) while one had multiple nuclei with positive staining for RAD51 (HR-proficient; Fig. 3). The RAD51 negative (HR-deficient) patient had a PFS of 10.2 months; this patient had discontinued treatment after 5 months due to AEs and subsequently died without documented progression. Notably, there was no known HRR gene alteration in this patient's tumor, however the patient did have a *CTNNB1* alteration in the Wnt signaling pathway. The RAD51-positive patient had stable disease for 5.7 months and subsequently discontinued treatment due to AEs without further follow-up of disease. A summary of the efficacy by HRR gene status is shown in Table 4.

Discussion

Our study sought to evaluate the safety profile and preliminary efficacy of olaparib when administered concurrently with radium-223. The dose escalation portion of this study determined that the RP2D of olaparib is 200 mg BID when given with radium-223. This study integrated biopsy results and genomic sequencing. There is indication of preliminary clinical benefit that will be further expanded in an ongoing phase II study. A similar study evaluating the safety profile of radium-223 in combination with niraparib, another PARPi, established that niraparib can be safely administered concurrently with radium-223 at specified doses of 100 mg and 200 mg orally daily for chemotherapy-exposed and chemotherapy-naïve patients, respectively (22).

A concern with concurrent PARPi and radium-223 is overlapping bone marrow toxicities given that both forms of therapy have independently been associated with evidence of marrow suppression. Large phase III studies have evaluated the toxicities of radium-223 and olaparib as monotherapies, ALSYMPCA (5) and PROfound (9) trials, respectively. The ALYSMPCA trial assessed radium-223 in men with mCRPC and bone metastases, and reported hematologic TRAEs of anemia (31% all grades, 13% grade 3 or higher), thrombocytopenia (12% all grades, 6% grade 3 or higher), and neutropenia (5% all grades, 3% grade 3 or higher). The PROfound study evaluated olaparib at 300 mg twice daily in men with mCRPC and a qualifying HRR gene alteration. Hematologic TRAEs were anemia (46% all grades, 21% grade 3 or higher), thrombocytopenia (<10% all grades, 3.5% grade 3 or higher), and neutropenia (<10% all grades, 3.9% grade 3, or higher). Of note, a significant portion of patients on these trials had received prior treatment with docetaxel (29% in PROfound and 58% in ALYSMPCA). In our study, AEs were amplified at the highest dose cohort of 300 mg twice daily, with the majority of 6 patients experiencing an AE of whom two experienced a grade 3 or higher hematologic AE. DL2 was clinically less tolerable, and thus a lower dose-level was set as RP2D. In total, 58% of patients experienced anemia of any grade (25% were grade 3 or higher), 42% had thrombocytopenia (8% grade 3 or higher), and 4% had leukopenia (no grade 3 or higher events). This AE profile is similar to that of olaparib alone and radium-223 alone as previously reported per PROfound and ALSYMPCA; decreased hemoglobin was ranked highest on reported side effects based on a retrospective toxicologic profiling (23). Ensuring a robust baseline hemoglobin and monitoring for hematologic toxicities with as-needed transfusions are important with this combination, which can safely be done as was demonstrated in our study.

Regarding clinical outcomes, 2 of 12 patients (1 patient at each dose level) demonstrated a PSA_{50}. However, there was a more robust alkaline phosphatase response that was observed in half of the patients in the entire cohort. These findings are in concordance with outcomes previously seen with radium-223, which is typically not associated with a PSA response, but can lead to decreases in alkaline phosphatase and improved OS in men with mCRPC (24). Findings from the ALSYMPCA trial did not report PSA_{50}, however there was a significant 30% or greater reduction in PSA levels at week 12 (16% of patients treated with radium-223 and 6% of patients treated with placebo, $P < 0.001$; ref. 5). PSA responses with olaparib are more predictable and can be more pronounced in cancers harboring certain HRR mutations such as *BRCA1/2* (25). Results from PROfound showed a PSA_{50} in 43%

of olaparib-treated patients harboring at least one alteration in *BRCA1*, *BRCA2*, or *ATM*. When olaparib-treated patients harboring any of 12 other prespecified genes involved in HRR were added to the analysis, PSA_{50} was only 30% (9). Treatment outcomes from this phase I study is purely descriptive in nature, and should be interpreted with the caveat that this is a small sample size with a heterogeneous patient population.

Our study used baseline tumor biopsies to interrogate HRR gene alterations in the study population. We were able to successfully execute our study with largely bone biopsies and use these specimens for genomic profiling. Nine patients had available tissue for profiling, and we observed an HRR rate of 22% which is concordant with published data (22, 20). Evaluating genetic aberrations in functional HRR is novel and unique compared with standard NGS (20). The OncoPanel biomarker data revealed 1 patient with a *CTNNB1* (*Wnt* signaling pathway) alteration whose tumor stained negative for RAD51 that was indicative of functional HRR deficiency. While this patient did not have a PSA response, time to treatment progression was 10.2 months. A larger cohort of patients is needed to fully understand and assess this association. Interestingly, the patient with functional HRR deficiency based on RAD51 demonstrated a longer PFS and highlights a potential alternative biomarker worth investigating to assess sensitivity to PARPi (26). While RAD51 status could not be assessed in the patient with a *BRCA2*-mutated tumor, this case was also associated with a prolonged PFS of 11.8 months, and PSA and alkaline phosphatase responses. Further research evaluating these biomarkers and whether they can predict responsiveness to combination PARPi and radiotherapy is needed, and can provide promising data regarding the importance of pretreatment NGS.

The phase I results reported herein require confirmation in a larger study and comparison with a control. These findings have prompted the continuation of this study to a phase II trial which is currently enrolling patients. This is a randomized, open-label trial to evaluate the combination of olaparib and radium-223 compared with radium-223 alone in men with mCRPC. The primary endpoint of the phase II trial is rPFS. HRR gene alteration status, which is an integral biomarker, will be retrospectively determined on tissue collected after randomization to allow for assessment of rPFS in HRR gene altered biomarker groups.

In conclusion, we report that olaparib can be safely combined with radium-223 at the RP2D 200 mg orally twice daily dosing for men with mCRPC with bone metastases. With hematologic toxicities being some of the most commonly identified AEs, there is a need for close laboratory monitoring on this regimen. In addition, further efficacy will be investigated in an ongoing phase II clinical trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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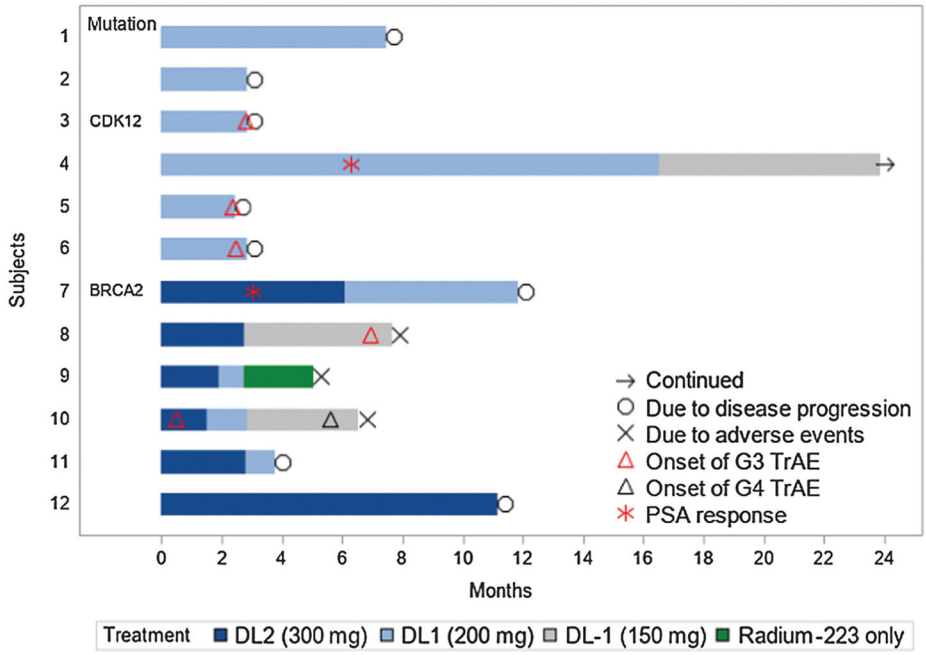

Figure 1.

Swimmer plot showing treatment dose, duration, reason off treatment, PSA_{50} response, and onset of grade 3 or 4 TRAEs.

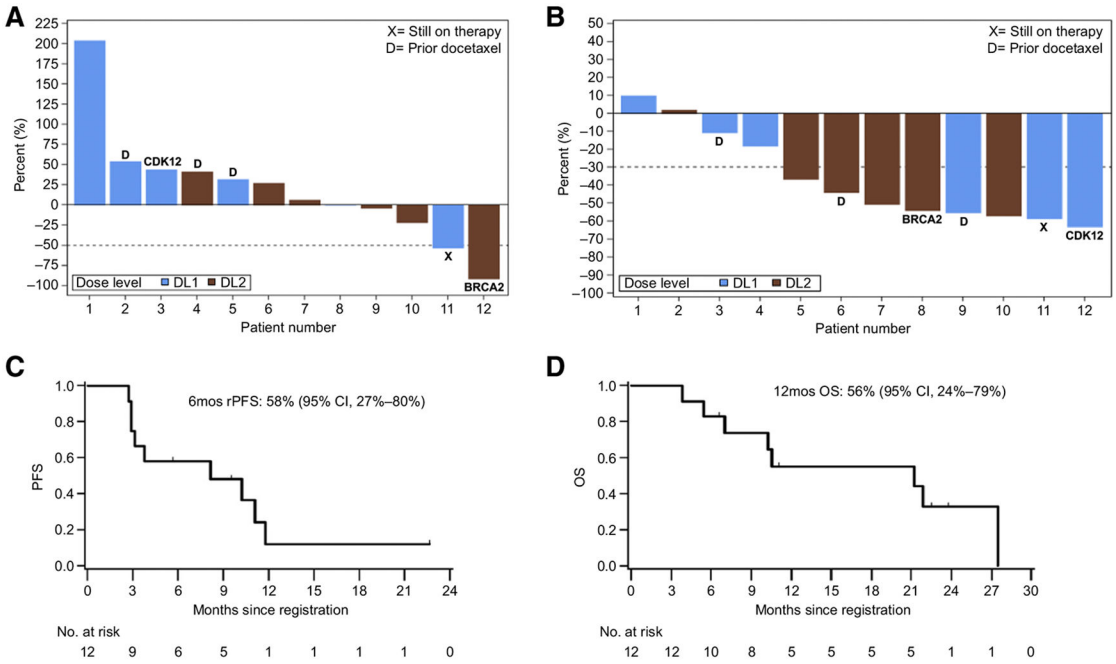

Figure 2.

Treatment outcomes. A waterfall plot showing the percent of PSA decline from baseline (**A**), and the percent of ALK decline from baseline (**B**). Kaplan–Meier estimate of rPFS (**C**) and OS (**D**).

A

Stain	USI	Geminin	RAD51	HR-status
RAD51	OAAEDP-0CFC57		Negative	HR-deficient
Geminin	OAAEDP-0CFC58	Positive		
RAD51	OAAEJD-0D56CH		Positive	HR-proficient
Geminin	OAAEJD-0D56CI	Positive		
RAD51	OAAEKR-0D56CN		Negative	N/A
Geminin	OAAEKR-0D56CO	Negative		
RAD51	OAAENI-0D56CK		Negative	N/A
Geminin	OAAENI-0D56CL	Negative		

B

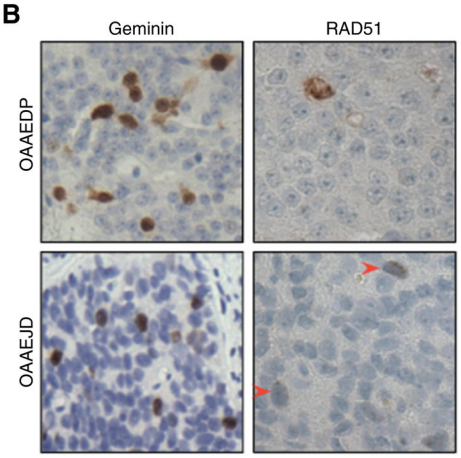

Figure 3.

RAD51 staining and HR-status of archival tumor samples. Serial sections of the samples listed in (**A**, USI) were stained using antibodies to Geminin or RAD51. Representative images of the stains are shown in (**B**). Among the four samples, optimal staining for Geminin was observed in samples OAAEDP and OAAEJD. Among these two samples, multiple nuclei in OAAEJD were RAD51-foci positive (red arrows) while there was no evidence of RAD51-foci positive nuclei in OAAEDP. There are two species of RAD51 in the nuclei, (1) RAD51 bound to DNA as a nucleo-proteo filament seen and foci and (2) unbound RAD51 that stains weakly pan-nuclear. The lower right panel in (**B)** shows the presence of both bound and unbound (weakly pan-nuclear), and the presence of foci suggests HR-proficiency. The upper right panel in (**B)** had no evidence of foci, and the stain sen is of a damaged nucleus and most likely non-specific stain. Therefore, OAAEDP is HR-deficient while OAAEJD is HR-proficient. HR-status of samples OAAEKR and OAAENI could not be assessed because both samples were negative for both Geminin and RAD51.

Table 1.

Patient enrollment, demographics, and baseline disease characteristics ($N = 12$).

	N	**%**
Race		
White	11	92
Unknown	1	8
ECOG performance status		
0	8	67
1	4	33
Prior treatment		
Docetaxel	3	25
ARSI[a]	12	100
Radiation[b]	9	75
Current use of bisphosphonates or denosumab at study entry		
No	2	17
Yes[c]	10	83
Baseline disease		
Measurable	3	25
Non-measurable only	9	75
Presence of lymph node lesions at baseline		
No	8	67
Yes	4	33
	Median	**Range**
Patient age at registration, year	68	59–81
Prior lines of CRPC therapies	2	1–5

[a]Abiraterone/Enzalutamide/Apalutamide.

[b]Radiation sites: prostate gland ($n = 5$), orbit ($n = 1$), vertebral and hip ($n = 1$), unknow($n = 2$).

[c]All 10 patients received denosumab.

Table 2.

Summary of TRAEs.

	DL1 (*N* = 6)			DL2 (*N* = 6)				Total (*N* = 12)
	G1	G2	G3	G1	G2	G3	G4	
AE type								
Fatigue	5	1		2	3			11(92%)
Anemia	1	1	**2**	1	1	**1**		7(58%)
Diarrhea	3			1	1			5(42%)
Nausea	2	1			2			5(42%)
Platelet count decreased	2		1	1	1			5(42%)
Anorexia	2			2				4(33%)
Lymphocyte count decreased					3		**1**	4(33%)
White blood cell decreased				2	2			4(33%)
Dyspepsia	2			1				3(25%)
Neutrophil count decreased		1			2			3(25%)
Dizziness	1			1				2(17%)
Vomiting	1			1				2(17%)
Creatinine increased				2				2(17%)
Dyspnea				2				2(17%)
Hoarseness	1							1(8%)
Paresthesia	1							1
Arthralgia	1							1
Generalized edema	1							1
Hyperglycemia				1				1
Stroke						1		1
Hypercalcemia					1			1
Hypertension					1			1
Dysgeusia				1				1
Generalized muscle weakness				1				1
Peripheral sensory neuropathy					1			1
Total Number of Event	23	4	3	19	18	2	1	70

Table 3.

PSA, ALK and RECIST response.

	DL1 (*N* = 6)		DL1 (*N* = 6)		Total (*N* = 12)	
	N	**%**	***N***	**%**	***N***	**%**
PSA_{50}						
Yes	1	16.7	1	16.7	2	16.7
ALK response (>30% decline)						
Yes	3	50.0	5	83.3	8	66.7
Radiographic best response						
SD	2	33.3	5	83.3	7	58.3
PD	4	66.7	1	16.7	5	41.7

Table 4.

Efficacy by HRR gene status.

Case	Prior Taxane	PSA Response	Alk Phos Response	Objective response	rPFS (months)	Alterations Status	Geminin	RAD51
1	N	N	N	SD	8.1	AR	–	–
2	Y	N	N	PD	2.9	None	–	–
3	N	N	Y	PD	3.1	CDK12	–	–
4	N	Y	Y	SD	11.8	BRCA2	–	–
5	N	N	Y	SD	9.5[a]	NA	–	–
6	Y	N	Y	SD	10.2	CTNNB1	Positive	Negative
7	N	N	N	SD	5.7[b]	None	Positive	Positive
8	N	N	Y	PD	3.7	None	Negative	Negative
9	N	N	Y	SD	11.0	None	Negative	Negative
10	N	Y	Y	SD	22.6[b]	NA	–	–
11	N	N	N	PD	2.7	NA	–	–
12	Y	N	Y	PD	2.9	None	–	–

Abbreviations: NA, Not available; PD, Progressive disease; SD, Stable disease.

[a]Patients were off treatment due to AEs without documented disease progression, censored at last disease assessment date.

[b]Still on therapy and progression-free at last follow-up.