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Brief Report

Olaparib and Durvalumab in Patients with DNA Damage Repair Alterations and Biochemically Recurrent Prostate Cancer

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INTRODUCTION

Patients who develop biochemically recurrent prostate cancer after definitive therapy to the prostate are viewed as having asymptomatic, micrometastatic disease. As such, balancing the toxicities of therapy with cancer control is a high priority. Androgen deprivation therapy (ADT) has been a standard of care for decades for patients with biochemical recurrence (BCR) at high risk for metastatic disease after definitive and salvage therapies.[1,2] More recently, the EMBARK trial demonstrated a metastasis-free survival benefit from ADT + enzalutamide, an androgen receptor inhibitor, versus ADT alone.[3] However, as ADT reduces muscle mass, decreases bone density, increases cardiovascular risk, and causes bothersome symptoms (hot flashes, fatigue, decreased libido),[4] there remains great interest in ADT-sparing or -limiting therapies.

The discovery that poly-ADP ribose polymerase (PARP) inhibition can impact tumors with pathologic

alterations in DNA damage repair (DDR) pathways has expanded treatment options in metastatic castration-resistant prostate cancer (mCRPC). A phase 2 study of the PARP inhibitor olaparib in combination with the anti–PD-L1 antibody durvalumab and ADT in patients with mCRPC identified responses in tumors harboring DDR alterations.[5] Cytosolic DNA damage activates the innate immune response via the stimulator of the interferon-gamma pathway[6]; the addition of an anti–PD-L1 agent further promotes an antitumor immune response. BCR may be more susceptible to immune activation than mCRPC, given a less immune suppressed tumor microenvironment.[7,8]

We hypothesized that PARP inhibition combined with an anti–PD-L1 inhibitor in mutation-selected patients with BCR could yield durable responses, defined as an undetectable prostate-specific antigen (PSA) with noncastrate testosterone levels. Furthermore, this combination could be tested initially as an ADT-sparing approach. In a disease fueled by testosterone, an undetectable PSA with noncastrate testosterone levels provides an early readout that a patient may even be cured of the disease.[9] Given the long natural history of BCR, the use of such interim endpoints is critical when assessing for early signals of the efficacy of combinations with curative potential.

METHODS

This was an open-label, single-arm clinical trial (ClinicalTrials.gov Identifier: NCT03810105) for patients with BCR prostate cancer. Patients were eligible if they had prior prostatectomy for prostate adenocarcinoma with or without prior salvage radiotherapy and a rising PSA at three time points obtained at least 1 week apart, minimum PSA of 0.50 ng/mL, and PSA doubling time of ≤ 9 months. Computed tomography (CT) or magnetic resonance imaging (MRI) and bone scan were used to determine nonmetastatic disease. Prior ADT (≤ 2 cycles) in the BCR setting was allowed, provided testosterone was $>$ 150ng/dL at enrollment. Qualifying DDR deleterious mutations (somatic or germline) included *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *FANCA*, *RAD51C*, *RAD51D*, *PALB2*, *BRIP1*, *BARD1*, and *CDK12*. Mismatch repair deficiency and high-tumor mutational burden were exclusionary. All patients were assessed using germline and somatic testing using MSK-IMPACT.[10] Patients provided informed consent to this institutional review board–approved study conducted in accordance with the Declaration of Helsinki. This was a multi-center study; all accruals occurred at Memorial Sloan Kettering Cancer Center.

Patients received olaparib 300 mg orally twice daily with durvalumab 1500 mg intravenous (IV) monthly for 24 cycles, providing an ongoing response. A cycle (C) was 28 days. If an undetectable level of PSA ($<$0.05) was not reached by C5, ADT with a GnRH analog (physician choice) was added for 6 months (C5–C11). Patients were monitored for adverse events using the Common Terminology Criteria for Adverse Events v4.0 and seen monthly during treatment and follow-up. Physical exams and laboratory assessments for toxicity, including complete blood count with differential, comprehensive metabolic panel, and thyroid function tests, in addition to PSA and testosterone, were performed. An end-of-treatment (EOT) visit occurred within 30 days of the last dose. Imaging using CT or MRI and bone scan was performed at baseline, C5, C24, or EOT if the patient discontinued treatment before C24. Peripheral blood mononuclear cells were collected at baseline, C5, C11, and EOT. Serial T-cell exhaustion/activation flow phenotyping and baseline myeloid-derived suppressor cells (MDSCs) were analyzed as previously described.[11,12]

The primary endpoint was an undetectable PSA with recovered testosterone at 24 months. Patients who did not meet the primary endpoint or had on-treatment PSA progression per Prostate Cancer Working Group 3 (PCWG3) criteria were removed from the study. Patients meeting the primary endpoint continued monitoring of PSA off treatment.

Thirty-two patients were planned for enrollment. If eight or more successes were observed, it would be concluded that the therapy is sufficiently active to warrant further study. This design had a power greater than 0.90 for a population success proportion of 0.35 using a one-sided test with a size of 0.10 for the population success rate of 0.15.

RESULTS

Five patients with prior prostatectomy, salvage radiotherapy, and BCR were enrolled between April 2019 and March 2021. The trial was closed early in March 2022 due to slow accrual, which was driven by the difficulty in identifying patients with BCR who also had deleterious DDR alterations. The median age was 70 years (range 52–79) and the Gleason score was 9 (range 7–9). The median PSA before the study treatment was 1.11 ng/mL (range 0.59–10.82). As no patient achieved an undetectable PSA by C5, 6 months of ADT was added. Two (40%) patients met the primary endpoint (Fig. 1). Patient 2 (somatic *BRCA2* [NM_000059] exon11 p.Q2164* [c.6490C>T]) has remained off therapy since trial completion, with an undetectable PSA and normal testosterone for 30 months during the follow-up period. His PSA recently became measurable and is being monitored. Patient 5 (somatic *ATM* [NM_000051] exon21 p.E1031* [c.3091G>T] and *ATM* [NM_000051] exon22 splicing variantp.X1052_splice [c.3154-1G>C]) has also remained off therapy after the completion of study treatment with an undetectable PSA with normal testosterone. Of the three patients who did not meet the primary endpoint, patient 3 came off the study early at C5 after developing a grade 2 rash and grade 1 creatinine elevation. The other two patients came off the study

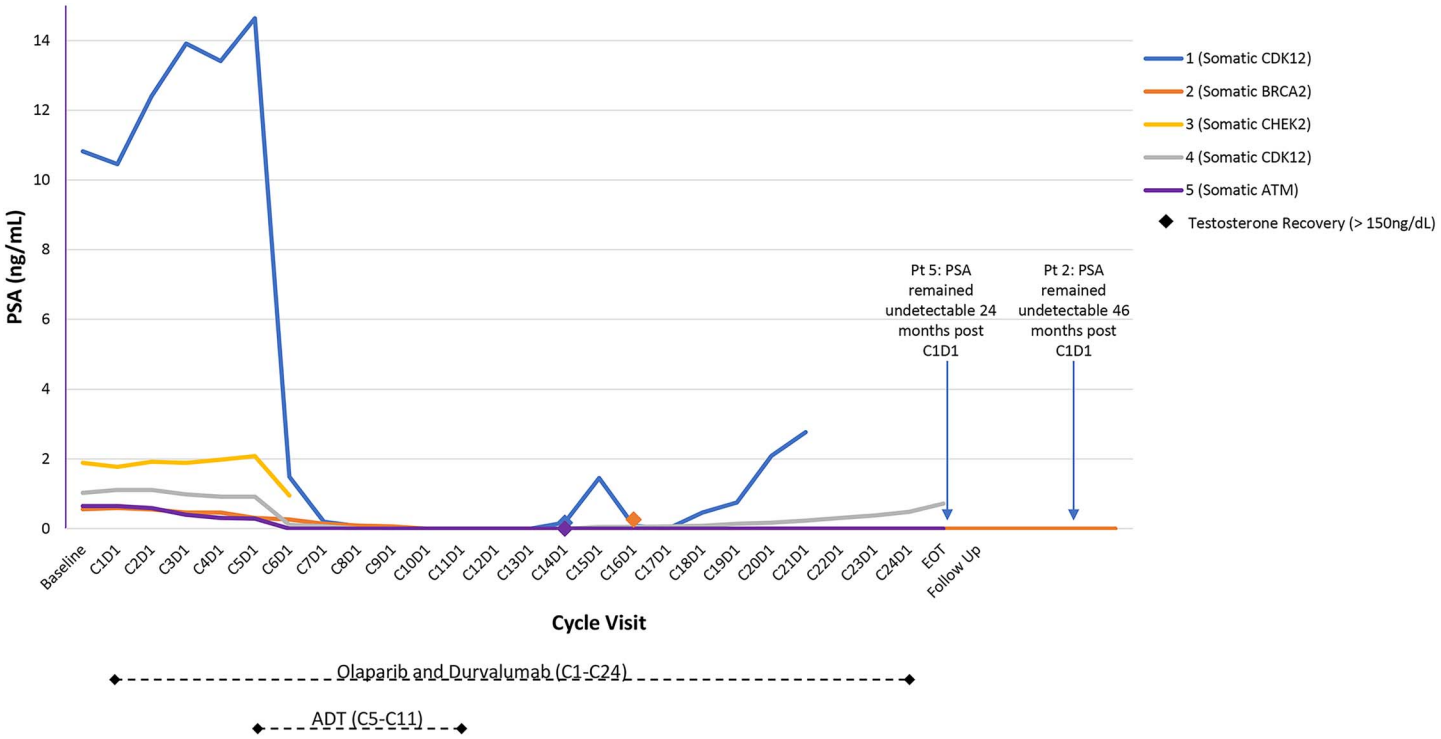

Figure 1. Prostate-specific antigen (PSA) responses in patients receiving durvalumab and olaparib with a short course of androgen deprivation therapy (ADT). Durable responses (defined by undetectable PSA) off all therapy and with recovered testosterone were seen in two patients.

because of rising PSA. Patient 4 discontinued with PSA progression at C24; his testosterone had recovered as of C14. Patient 1 completed 20 cycles of therapy before discontinuing for PSA progression; his testosterone recovery also occurred at C14.

Adverse events are listed in Table 1. Immune-related adverse events included grade 1 infusion-related reaction ($n = 1$), grade 1–2 pruritis ($n = 2$), grade 2 psoriasiform rash ($n = 1$), grade 3 hyperglycemia ($n = 1$), grade 2 hypothyroidism ($n = 1$), and grade 1–2 diarrhea ($n = 2$); none required systemic corticosteroids. One patient stopped treatment for Grade 2 psoriasiform rash and grade 1 creatinine elevation.

Peripheral blood mononuclear cell samples ($n = 22$) were analyzed using T-cell activation or exhaustion and MDSC flow phenotyping panels. CD14+HLA-DR^{lo}Lin^{-} MDSCs as a percentage of all live lymphocytes or monocytes were measured at baseline. The two responders had lower levels of baseline MDSCs relative to other patients. Additionally, patient 2 (responder) had markedly higher levels of plasma interleukin-2 throughout treatment, higher frequencies of Ki67+ proliferating CD8 T cells at baseline, decreased frequencies of Ki67+, ICOS+ T cells, and a sustained decrease in FoxP3+CTLA-4+ CD4 regulatory phenotype T cells while on treatment (Fig. 2).

DISCUSSION

ADT-sparing regimens for BCR are appealing strategies to avoid the toxicities of androgen deprivation, although many contemporary trials intensify androgen inhibition in this population. Systemic therapies can prolong metastasis-free survival in high-risk BCR but are noncurative in this patient population with a long natural history. In this series, PARP inhibition plus anti–PD-L1 without ADT was unable to lower PSA to undetectable levels, potentially because more tumor apoptosis was required using ADT to increase reliance on PARP and evoke synthetic lethality; however, with the addition of ADT, two patients (40%) maintained an undetectable PSA during follow-up with full testosterone recovery and off all therapy. The toxicity profile of olaparib and durvalumab seen in this trial was consistent with prior research on these agents.[5]

BCR represents a heterogeneous population, and patients with high-risk features (e.g., fast PSA doubling time) are generally considered for systemic therapy trials or ADT in clinical practice. However, the landscape of treatment options for high-risk BCR is evolving. For decades, ADT as monotherapy was used when systemic therapy was warranted; however, as the field identified that hormone intensification with ADT in combination with androgen receptor pathway inhibitors benefited patients with metastatic hormone-sensitive prostate cancer, clinical trials opened in the BCR space (e.g., NCT02319837, NCT03009981). The EMBARK trial demonstrated a metastasis-free survival advantage for those patients receiving ADT plus enzalutamide over ADT alone. In parallel to these efforts in BCR is research aimed at de-intensification or the avoidance of ADT. Targeted therapy

Table 1. Adverse events in patients with biochemically recurrent prostate cancer ($N = 5$)

	n (%)			
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**All Grades**
Cardiac disorders				
Sinus bradycardia	1 (20)	0 (0)	0 (0)	1 (20)
Ear and labyrinth disorders				
Vertigo	1 (20)	0 (0)	0 (0)	1 (20)
Endocrine disorders				
Hypothyroidism	0 (0)	1 (20)	0 (0)	1 (20)
Hyperglycemia	0 (0)	0 (0)	1 (20)	1 (20)
Eye disorders				
Chalazion	1 (20)	0 (0)	0 (0)	1 (20)
Gastrointestinal disorders				
Constipation	1 (20)	0 (0)	0 (0)	1 (20)
Diarrhea	0 (0)	2 (40)	0 (0)	2 (40)
Dyspepsia	1 (20)	0 (0)	0 (0)	1 (20)
Gastroesophageal reflux disease	1 (20)	0 (0)	0 (0)	1 (20)
Nausea	1 (20)	0 (0)	0 (0)	1 (20)
Dysgeusia	1 (20)	0 (0)	0 (0)	1 (20)
General disorders				
Fatigue	1 (20)	1 (20)	0 (0)	2 (40)
Pain	1 (20)	0 (0)	0 (0)	1 (20)
Infusion-related reaction	1 (20)	0 (0)	0 (0)	1 (20)
Infection				
Mucosal infection	1 (20)	0 (0)	0 (0)	1 (20)
Right eye with stye	1 (20)	0 (0)	0 (0)	1 (20)
Musculoskeletal				
Arthralgia	1 (20)	1 (20)	0 (0)	2 (40)
Back pain	0 (0)	0 (0)	0 (0)	0 (0)
Neck pain	1 (20	0 (0)	0 (0)	1 (20)
Nervous system disorders				
Headache	1 (20)	0 (0)	0 (0)	1 (20)
Neuropathy	1 (20)	0 (0)	0 (0)	1 (20)
Renal disorders				
Hematuria	1 (20)	0 (0)	0 (0)	1 (20)
Pollakiuria	0 (0)	1 (20)	0 (0)	1 (20)
Blood creatinine elevation	1 (20)	0 (0)	0 (0)	1 (20)
Respiratory				
Cough	1 (20)	0 (0)	0 (0)	1 (20)
Dyspnea	1 (20)	0 (0)	0 (0)	1 (20)
Nasal congestion	1 (20)	0 (0)	0 (0)	1 (20)
Skin/dermatologic conditions				
Psoriasis	0 (0)	1 (20)	0 (0)	1 (20)
Pruritis	1 (20)	0 (0)	0 (0)	1 (20)
Rash maculo-papular	1 (20)	0 (0)	0 (0)	1 (20)
Vascular disorders				
Embolism	0 (0)	1 (20)	0 (0)	1 (20)
Hypertension	1 (20)	0 (0)	0 (0)	1 (20)

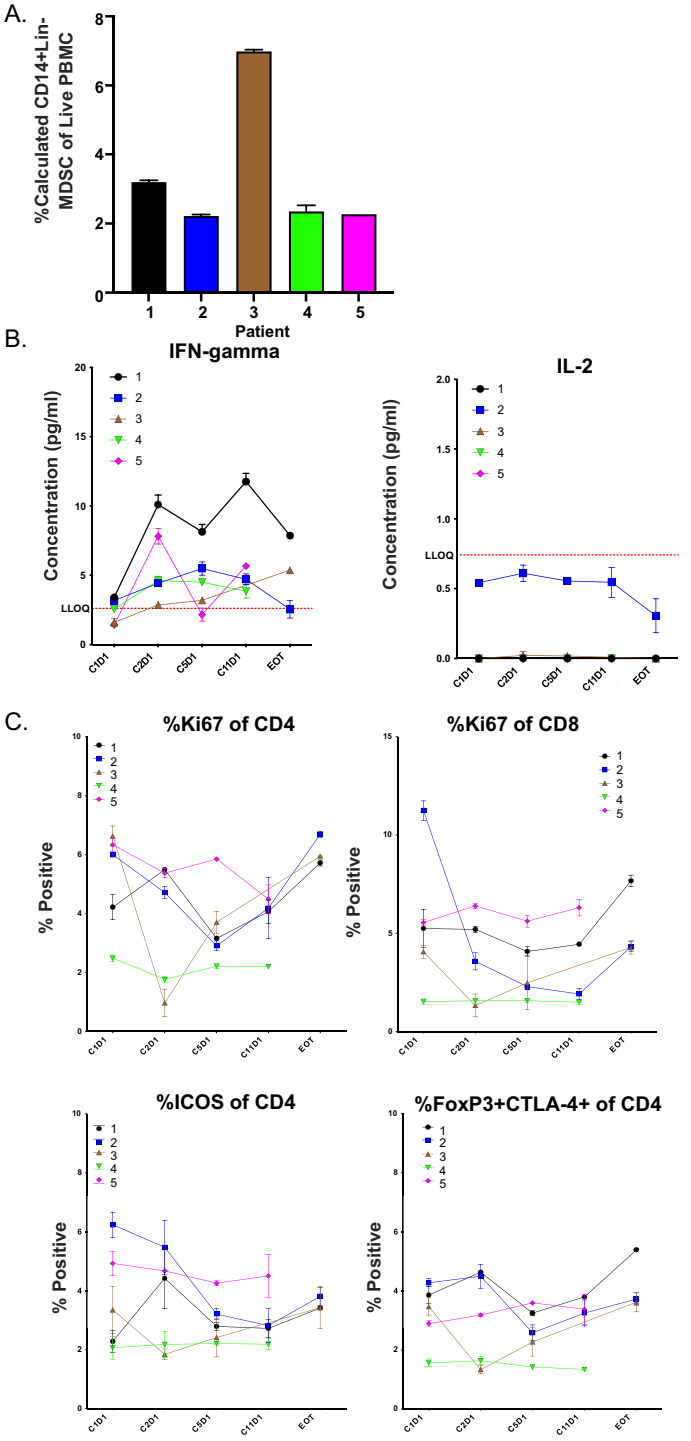

Figure 2. Peripheral immune correlatives. (A) Baseline myeloid-derived suppressor cells (MDSC) frequency. (B) Longitudinal plasma cytokine measurements. (C) Peripheral T-cell flow phenotyping across treatment visits. C1D1 reflects baseline before treatment with olaparib and durvalumab. Androgen deprivation therapy (ADT) was added at C5D1 and continued until C11. Patients 2 and 5 met the primary endpoint (undetectable prostate-specific antigen [PSA] with recovered testosterone). C: cycle; CD: cluster of differentiation; CTLA4: cytotoxic T-lymphocyte-associated protein 4; D: day; EOT: end of treatment; ICOS: inducible costimulator; IFN: interferon; IL2: interleukin 2; FOXP3: forkhead box P3; Ki67: marker of proliferation Kiel 67; PBMC: peripheral blood mononuclear cells.

for those with genomic alterations is a logical extension of ADT-sparing research, given the positive results of trials of PARP inhibition in mCRPC.[13,14]

A recent study of olaparib monotherapy in BCR found that 48% (13/27) of patients with DDR alterations achieved a 50% PSA decline (PSA50) on treatment, while another trial of rucaparib monotherapy in DDR-positive BCR demonstrated that 28% (2/7) achieved an

undetectable PSA while on therapy.[15,16] Collectively, this suggests that targeted therapy alone can yield favorable responses in mutation-selected patients. Our study is limited in interpretation because of the small cohort size and lack of a control group. However, it is the first to report the durability of response as measured by an undetectable PSA off all therapy with a combination of targeted therapy and immunotherapy approaches in mutation-selected patients with BCR. This combination had previously been demonstrated to be safe and effective in patients with mCRPC in a phase 2 trial and has also been evaluated in other solid tumors such as germline BRCA1/2 ovarian and breast cancers (NCT02734004).[5]

The two patients who met the primary endpoint (undetectable PSA with recovered testosterone) had fewer MDSCs at baseline; MDSCs reflect an immune-suppressive tumor microenvironment. Higher numbers of MDSCs have been associated with a worse prognosis, lack of response to combination PARP inhibition plus anti–PD-L1 in mCRPC, and lower response to anti–PD-L1 in other solid tumors where checkpoint inhibitors are approved.[17,18] It is plausible that the lower baseline MDSC in the two responders contributed to their response.

Can precision medicine mitigate the need for ADT in BCR? In this limited experience, we demonstrated that durvalumab and olaparib, plus a short course of ADT, yielded remissions that persisted beyond what would be expected from ADT alone. Future studies with trial designs evaluating novel therapies without ADT in BCR may ultimately identify populations for which ADT-sparing or -limiting approaches are effective.

Data Availability

Data sharing is available to bona fide researchers by contacting the corresponding author.

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