Editorial Commentary

Rucaparib monotherapy in the heavily pre-treated metastatic castrate-resistant prostate cancer setting: practical considerations and alternate treatment approaches

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Over the past few years, poly-ADP ribose polymerase inhibitors (PARPi) have emerged as a guideline-approved, biomarker-selected treatment approach for the management of metastatic castrate-resistant prostate cancer (mCRPC). Following the publication of multiple trials in this disease space, numerous such agents, either alone or in combination with androgen receptor pathway inhibitors (ARPI) have gained Food and Drug Administration (FDA) approval across the mCRPC treatment paradigm (*Figure 1*): (I) rucaparib in May 2020 for mCRPC patients with deleterious BReast CAncer (*BRCA*) mutations who had been previously treated with an ARPI and taxane-based chemotherapy (1) [TRITON2 (2)]; (II) olaparib in May 2020 for patients with deleterious or suspected homologous recombination repair (HRR) gene-mutated mCRPC with progression following prior abiraterone or enzalutamide (3) [PROfound (4)]; (III) olaparib in combination with abiraterone and prednisone (or prednisolone) in May 2023 for mCRPC patients with deleterious or suspected deleterious *BRCA* mutations (5) [PROpel (6)]; (IV) talazoparib in combination with enzalutamide in June 2023 for mCRPC patients with HRR gene mutations (7) [TALAPRO-2 (8)]; and (V) niraparib in combination with abiraterone acetate plus prednisone in August 2023 for mCRPC patients with deleterious or suspected deleterious *BRCA* mutations (9) [MAGNITUDE (10)].

Updated, final results of TRITON2 were recently published by Abida *et al.* (11). To summarize, this is an international, open-label, phase II trial that evaluated the safety and efficacy of rucaparib 600 mg twice daily in mCRPC patients with DNA damage response (DDR) gene alterations who had progressed after one to two lines of an ARPI and one-taxane based chemotherapy. The efficacy cohort included 277 patients, of whom 172 (62.1%) had a deleterious germline or somatic *BRCA* alteration with 59 (21.3%), 15 (5.4%), seven (2.5%), 11 (4.0%), and 13 (4.7%) having ataxia-telangiectasia mutated gene (*ATM*), cyclin-dependent kinase 12 (*CDK12*), checkpoint kinase 2 (*CHEK2*), partner and localizer of BRCA2 (*PALB2*), and other DDR gene mutations, respectively. A confirmed objective response was observed in 46% of *BRCA* patients with measurable disease (complete response: 10%). A superior response was observed among *BRCA2* patients (48% versus 30% for *BRCA1*), which is potentially secondary to an increased frequency of biallelic mutations among *BRCA2* patients and a greater coexistence of *TP53* mutations among *BRCA1*-mutated men (12). Objective response was consistent irrespective of whether the *BRCA* mutation was somatic or germline and whether other DDR mutations were present or absent. All four patients with *PALB2* mutations and measurable disease had an objective partial response, with none of the *ATM*-, *CDK12*-, *CHEK2*-mutated patients experiencing an objective response. A

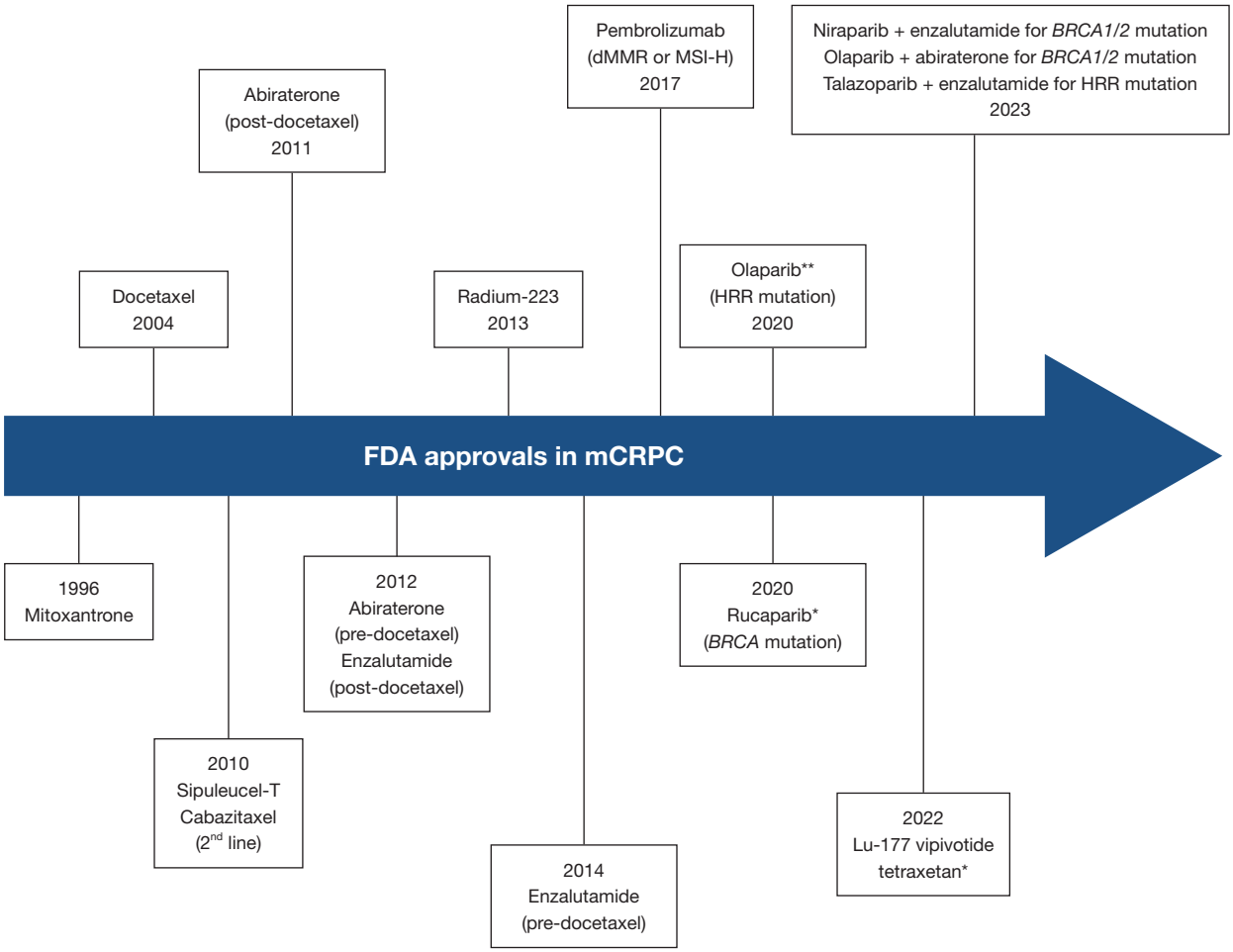

Figure 1 Current United States FDA-approved drugs in the metastatic castrate-resistant prostate cancer space. *, progressed following androgen-axis targeted treatment and taxane-based chemotherapy; **, progressed following treatment with enzalutamide or abiraterone. dMMR, DNA mismatch repair deficiency; MSI-H, microsatellite instability high; *BRCA*, BReast CAncer; HRR, homologous recombination repair; FDA, Food and Drug Administration; mCRPC, metastatic castrate-resistant prostate cancer.

confirmed prostate-specific antigen (PSA) response with ≥50% decrease from baseline (PSA50) was observed in 53% and 55% of *BRCA* and *PALB2*-mutated patients, compared to 3.4–14% among patients with other DDR gene mutations. The median overall survival was 17.2 months for *BRCA* patients, compared to 11.1–14.6 months among *ATM*, *CDK12*, and *CHEK2*-mutated patients (*Table 1*). Grade 3 or worse treatment-emergent adverse events were observed in 64% of patients, with the most common being anemia/decreased hemoglobin (29%) and fatigue (11%). Significantly, 33% of patients required at least one transfusion. While not reported in the TRITON2 overall safety population, known potential long-term sequalae of these agents, particularly if used in earlier settings, include myelodysplastic syndrome and bone marrow failure (13).

These results add to the existing evidentiary base for rucaparib in the mCRPC disease space, with the recently published TRITON3 phase III trial demonstrating that rucaparib 600 mg twice daily in mCRPC patients with a *BRCA* or *ATM* alteration and who had disease progression following treatment with an ARPI improved imaging-based progression-free survival from a median of 6.4 to 10.2 months [P<0.001; (14)]. These results 'move up' rucaparib along the mCRPC treatment paradigm from the 3rd to 2nd line setting. As with other drugs in this disease space, such as docetaxel and ARPIs, there is a concerted effort to move up these agents further up the prostate cancer treatment landscape. Ongoing phase III trials in the metastatic hormone sensitive

Table 1 Summary of efficacy results by gene alteration from TRITON2

Outcome	*BRCA1* (n=22)	*BRCA2* (n=150)	*ATM* (n=59)	*CDK12* (n=15)	*CHEK2* (n=7)	*PALB2* (n=11)	Other (n=13)
ORR (%)	30	48	0	0	0	100	25
DoR, median (months)	15.5		–	–	–	10.1	–
rPFS, median (months)	10.7		5.3	–	–	13.6	5.8
PSA50 (%)	18	59	3.40	6.70	14	55	23
PSA90 (%)	20		0	0	14	9.10	23
Time to PSA progression (months)	6.5		3.1	–	–	7.5	–
OS, median (months)	17.2		14.6	13.9	11.1	17.7	10.5

BRCA, BReast CAncer; *ATM*, ataxia-telangiectasia mutated gene; *CDK12*, cyclin-dependent kinase 12; *CHEK2*, checkpoint kinase 2; *PALB2*, partner and localizer of BRCA2; ORR, objective response rate; DoR, duration of response; rPFS, radiographic progression-free survival; PSA50, 50% decrease in PSA level; PSA90, 90% decrease in PSA level; PSA, prostate-specific antigen; OS, overall survival.

prostate cancer (mHSPC) space include TALAPRO-3 (NCT04821622), evaluating the combination of talazoparib plus enzalutamide, and AMPLITUDE (NCT04497844), evaluating the combination of niraparib plus abiraterone, both in mHSPC patients with HRR gene alterations. The phase II ZZ-First (NCT04332744) trial is evaluating the addition of talazoparib to enzalutamide in unselected mHSPC patients. In the high-risk localized and locally advanced setting, the NADIR (NCT04037254) three-arm trial is comparing radiotherapy + androgen deprivation therapy (ADT) to each of niraparib alone and niraparib + radiotherapy/ADT. Results of these trials are expected to become available in the next few years and will determine where PARP inhibitors will ultimately fit in the prostate cancer treatment landscape.

The efficacy of rucaparib in TRITON2 highlights its potential role in the post-ARPI/docetaxel setting and adds to the multitude of treatment options for patients in the '3rd line' treatment setting, which also includes cabazitaxel and lutetium-177 (^{177}Lu)-PSMA-617. The optimal treatment approach for patients in this setting remains uncertain. While it is currently recommended that all patients with metastatic prostate cancer undergo testing for germline and somatic tumor mutations, with patients harboring actionable mutations such as *BRCA1/2* ideally benefiting from a biomarker-selected treatment approach with PARPi, the reality is that the majority of patients in clinical practice do not undergo genetic testing (15,16). Another complicating factor is that the best method for detecting an HRR deficiency has yet to be determined. While obtaining genetic testing from a fresh metastatic tumor biopsy is considered optimal, it is often unavailable and can be technically challenging to obtain in select metastatic cases (e.g., bone biopsy samples). Use of circulating tumor DNA remains an option in this setting, along with an archival sample of metastatic or primary tumor tissue, although limitations in this scenario include longitudinal accumulation of additional somatic mutations that are not present in this older sample, multifocal/multiclonal disease not representative of other tumor sites, potential degradation of DNA after years in paraffin, and potential false positive results secondary to clonal hematopoiesis of indeterminate potential (CHIP). Reliance on blood or saliva samples for germline testing does not evaluate for somatic alterations and cannot discern monoallelic from biallelic alterations, missing approximately half of actionable *BRCA1/2* alterations.

Given the challenges associated with routine genetic testing in clinical practice, this may consequentially lead to the 'practical' utilization of ^{177}Lu-PSMA-617 and cabazitaxel in mCRPC patients progressing following prior APRI and docetaxel treatment (17,18). Both agents have demonstrated overall survival benefits in this setting and their use may be applicable to a broader population of mCRPC patients. In TheraP, eligible patients were required to have high expression on prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT), with at least one site with a maximum standardized uptake value (SUVmax) ≥20) and no sites of fluorodeoxyglucose (FDG)-positive/PSMA-negative disease. Based on these criteria, 200/291 patients (68.7%) were eligible for study inclusion (18). Conversely in the VISION trial, patients were required to have PSMA-positive disease on the basis of a central review of ^{68}Ga-

PSMA-11 staging scans, with PSMA positivity defined as uptake greater in the metastatic lesions than in the liver. Further, they could have no PSMA-negative metastatic lesions. Of 1,003 scanned patients, 869 (86.6%) were deemed trial eligible (19). Given the increased availability and utilization of prostate-specific PSMA-PET/CT, along with most mCRPC patients expressing PSMA-positive disease in the post-ARPI/docetaxel setting, we may observe ^{177}Lu-PSMA-617 being preferentially utilized in this setting. Additionally, as of current, no biomarker testing is required prior to cabazitaxel administration.

In conclusion, we note that the results of the TRITON2 trial are an important addition to the current mCRPC literature and solidify rucaparib as a treatment option for mCRPC patients with disease progression following ARPI and docetaxel treatment. With the increased availability of treatment options in this disease setting, a nuanced approach to the management of these patients will be required to enhance guideline-concordant exposure to the maximal possible number of lines of therapy with alternate mechanisms of action in order to maximize survival outcomes in this high-risk population.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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