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Clinical

Navigating therapeutic sequencing in the metastatic castration-resistant prostate cancer patient journey

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BACKGROUND: Novel therapies for metastatic castration-resistant prostate cancer (mCRPC) have improved patient outcomes. However, there is uncertainty on the optimal selection of therapeutic agents for subsequent lines of therapy.
METHODS: We conducted a comprehensive review of published evidence from pivotal clinical trials and recent guidelines for the treatment of mCRPC. We further identify gaps in knowledge and areas for future research.
RESULTS: Key considerations to help guide treatment selection for patients with mCRPC include personal treatment history, individual clinical characteristics, symptoms, prognosis, availability of clinical trials, and other patient-specific factors. Genetic testing and prostate-specific membrane antigen-targeted imaging are important tools to evaluate candidacy for newer therapeutic options such as poly (ADP-ribose) polymerase inhibitors, alone or in combination with androgen receptor pathway inhibitors, and [^{177}Lu]Lu-PSMA-617.
CONCLUSION: This article provides an overview of the evolving treatment landscape of mCRPC, discussing guideline-recommended treatment options and data from key clinical trials, while highlighting ongoing trials that may impact the future treatment landscape. Recommendations for optimal treatment sequencing based on individual patient factors are provided.

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INTRODUCTION

In the United States (US), prostate cancer (PC) is the most frequently diagnosed cancer in men, representing 14% of all new cancer cases [1]. Approximately 8% of patients with PC have metastatic disease at diagnosis, and rates of de novo metastatic disease are increasing [2]. Initial treatment for metastatic or biochemically recurrent PC typically includes androgen deprivation therapy (ADT), often combined with an androgen receptor pathway inhibitor (ARPI) ± docetaxel [3–5]. Despite treatment, patients often experience disease progression while maintaining castrate levels of serum testosterone, either with metastases (metastatic castration-resistant PC [CRPC]; mCRPC) or without metastases (non-metastatic/M0 CRPC) [6].

Numerous life-prolonging therapies with novel mechanisms of action (MoAs) have been approved for the treatment of mCRPC [7–17]. In the US, these include taxane-based chemotherapy (docetaxel and cabazitaxel), ARPIs (enzalutamide and abiraterone acetate), radiopharmaceuticals (radium-223 and prostate-specific membrane antigen [PSMA]-targeted lutetium Lu-177 vipivotide tetraxetan, i.e., [^{177}Lu]Lu-PSMA-617), poly-ADP ribose polymerase (PARP) inhibitors (olaparib, rucaparib, niraparib, and talazoparib), and immunotherapies (sipuleucel-T and pembrolizumab) (Table 1) [7–18]. Additionally, metastasis-directed therapy, such as stereotactic body radiation therapy (SBRT), can be considered in select cases of oligoprogressive disease [19]. Although improvements in clinical outcomes have been observed with novel therapies [20–31], their approval has resulted in uncertainties on optimal treatment sequencing, and utilization of these treatments is limited, demonstrating the need for improved real-world treatment practices.

Therapies previously reserved for mCRPC have been expanded to earlier PC stages, including metastatic hormone-sensitive PC (mHSPC) and M0 CRPC, impacting treatment selection in mCRPC [3]. As ARPIs are now a standard of care (SOC) for both mHSPC and M0 CRPC, many patients will have experienced disease progression on both ADT and an ARPI when diagnosed with mCRPC [3]. The further adoption of triplet therapy (first-line docetaxel plus ARPI plus ADT) as a SOC for patients with mHSPC means that many patients will be exposed to both an ARPI and docetaxel before developing castration-resistant prostate cancer (CRPC) [32]. To overcome neoplastic biologic resistance and maximize clinical efficacy, therapies with a different MoA from previously utilized treatments should be selected [33, 34]. Therefore, accessibility and applicability of therapies within the pre-mCRPC space influence the availability and efficacy of treatments for mCRPC. In real-world practice, many patients with mHSPC still receive ADT monotherapy with rates of treatment intensification with docetaxel or ARPI ranging from 9.3% to 38.1% in a recent systematic review [35].

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Table 1. Current FDA-approved systemic therapies for mCRPC.

Mechanism of action	Drug	Specific indications or restrictions in the mCRPC setting	Key trials
ARPI	Abiraterone [7]	None	COU-AA-301 [20] COU-AA-302 [100]
	Enzalutamide [8]	None	AFFIRM [21]
Taxane chemotherapy	Docetaxel [9]	None	TAX 327 [92]
	Cabazitaxel [10]	After docetaxel	EFC6193/TROPIC [22]
Radiopharmaceutical (alpha emitter)	Radium-223 [11]	Symptomatic bone metastases with no visceral metastases	ALSYMPCA [23]
Cell-based immunotherapy	Sipuleucel-T [12]	Asymptomatic or minimally symptomatic disease	IMPACT [24]
Radiopharmaceutical (PSMA-targeted radioligand)	[^{177}Lu]Lu-PSMA-617 [13]	PSMA-positive metastatic disease; prior treatment with ARPI and taxane	VISION [25]
PARP inhibitor	Olaparib [14]	Monotherapy: HRR-mutated; after ARPI In combination with abiraterone: *BRCA*-mutated	PROfound [58] PROpel [26, 60]
	Rucaparib [15]	*BRCA*-mutated; after ARPI and docetaxel	TRITON2 [27]
	Talazoparib [18]	In combination with enzalutamide: HRR-mutated	TALAPRO-2 [28]
	Niraparib [16]	In combination with abiraterone: *BRCA*-mutated	MAGNITUDE [29]
Immune checkpoint inhibitor	Pembrolizumab [17]	MSI-H, dMMR, TMB ≥ 10 mutations/megabase (tumor-agnostic)	Retrospective studies [31, 68]

ARPI androgen receptor pathway inhibitor, *BRCA* breast cancer gene, *dMMR* deficient mismatch repair, *FDA* Food and Drug Administration, *HRR* homologous recombination repair, *Lu* lutetium, *mCRPC* metastatic castration-resistant prostate cancer, *MSI-H* microsatellite instability-high, *PARP* poly (ADP-ribose) polymerase, *PSMA* prostate-specific membrane antigen, *TMB* tumor mutational burden.

The importance of treatment sequencing is notable in real-world data examining mCRPC treatment patterns, as median OS lessens following each line of therapy [36]. Moreover, approximately half of patients treated for mCRPC receive ≥1 line of therapy [36]. In addition to clinical and patient-specific factors, accessibility of and information from genetic testing and molecular imaging expand the available information for decision-making.

This article reviews the evolving treatment landscape for mCRPC and provides recommendations for optimal treatment sequencing.

TREATMENT RECOMMENDATIONS AND PRACTICE

Various guidelines provide treatment recommendations for mCRPC, including the American Society of Clinical Oncology, American Urological Association, Society of Urologic Oncology, National Comprehensive Cancer Network® (NCCN®), European Society for Medical Oncology, and European Association of Urology (Table 2) [3, 37–40]. Optimal therapy selection should be individualized, based on critical patient and disease factors.

General principles for treatment selection

Key considerations for treatment selection include personal treatment history, individual disease characteristics, prognosis, and patient-specific factors (Fig. 1). Generally, selecting treatments with a novel MoA reduces cross-resistance and improves the likelihood of clinical benefit, with the exception of taxane-based chemotherapy [41]. Despite frequent use in real-world settings, switching to a second ARPI after disease progression on a first-line ARPI has limited efficacy [33, 34]. The effectiveness of re-treatment with docetaxel, following docetaxel- and ARPI-based treatment combinations in the mHSPC setting, has also been challenged, but may be dependent on the timing of progression after initial docetaxel treatment [42].

In tumor characteristics should be considered/tumor characteristics should be considered.

Pattern of disease spread and associated symptoms

The pattern of metastatic spread can provide insight into disease behavior, influencing treatment selection [43, 44]. Visceral metastases, specifically liver metastases, can be predictive of more aggressive disease biology and shorter survival observed with ARPIs and chemotherapy, vs patients without liver metastases [43, 44]. Although often classified together as visceral metastases, patients with lung metastases have a more favorable prognosis vs patients with liver metastases [43]. In patients with liver metastases, treatment with microtubule inhibitor chemotherapy, either docetaxel (if not received previously) or cabazitaxel, is generally preferred [3]. A phase 2 trial (NCT02254785) including patients with ARPI-naïve mCRPC and poor prognostic features (including liver metastases) demonstrated a higher clinical benefit rate with cabazitaxel vs physician's choice of enzalutamide or abiraterone [45]. Radium-223 (a bone-directed alpha emitter) can be considered for patients with symptomatic, bone-predominant metastatic disease without visceral metastases [23]. Of note, except for concurrent ADT and bone-targeting agents, radium-223 is not recommended for use as a combination therapy, given the increased fracture rates seen when administered with abiraterone [3]. Alternatively, the active cellular immunotherapy sipuleucel-T can be considered for patients with asymptomatic to minimally symptomatic disease without visceral metastases [24]. Although the pattern of metastasis may determine patient eligibility [23, 24, 43, 44], decisions on when to incorporate these therapies must consider all available options.

In patients with disease oligoprogression on systemic therapy, metastasis-directed therapy (radiotherapy delivery to metastatic lesions) can be considered, but there are limited data on this strategy in mCRPC [19, 30, 46, 47]. In the phase 2 ARTO trial, abiraterone plus SBRT improved prostate-specific antigen (PSA)-based outcomes and progression-free survival (PFS) vs abiraterone alone in patients with oligometastatic CRPC [19]. In the single-arm phase 2 TRAP trial, patients with oligoprogressive CRPC (with ≤2 progressive lesions that developed while on ARPI treatment)

Table 2. Guideline-recommended therapies in mCRPC and their pivotal trials.

Drug	Clinical trial name	Comparator	Study population	Results for primary endpoint(s)
Abiraterone	COU-AA-301 (NCT00638690)	Placebo	mCRPC with prior docetaxel	OS, median 15.8 months (abiraterone) vs 11.2 months (placebo), HR 0.74; 95% CI 0.64–0.86; $p < 0.0001$ [101]
	COU-AA-302 (NCT00887198)	Placebo	mCRPC without prior docetaxel	OS, median 34.7 months (abiraterone) vs 30.3 months (placebo); HR 0.81; 95% CI 0.70–0.93; $p = 0.003$ [102]
Enzalutamide	AFFIRM (NCT00974311)	Placebo	mCRPC with prior docetaxel	OS, median 18.4 months (enzalutamide) vs 13.6 months (placebo); HR 0.63; 95% CI 0.53–0.75; $p < 0.001$ [21]
	PREVAIL (NCT01212991)	Placebo	mCRPC without prior docetaxel	OS, median 32.4 months (enzalutamide) vs 30.2 months (placebo); HR 0.71; 95% CI 0.60–0.84; $p < 0.0001$ [103]
Docetaxel	TAX 327 (NCT00675545)	Mitoxantrone	mCRPC	OS, median 19.2 months (docetaxel) vs 16.3 months (mitoxantrone); HR 0.79; 95% CI 0.67–0.93; $p = 0.004$ [92]
Cabazitaxel	TROPIC (NCT00417079)	Mitoxantrone	mCRPC with prior docetaxel	OS, 15.1 months (cabazitaxel) vs 12.7 months (mitoxantrone); HR 0.70; 95% CI 0.59–0.83; $p < 0.001$ [22]
	CARD (NCT02485691)	ARPI (abiraterone or enzalutamide)	mCRPC with prior ARPI and docetaxel	OS, 13.6 months (cabazitaxel) vs 11.0 months (ARPI); HR 0.64; 95% CI 0.46–0.89; $p = 0.008$ [104]
Radium-223	ALSYMPCA (NCT00699751)	Placebo	mCRPC with ≥2 bone metastases and no visceral metastases; received prior docetaxel if able	OS, median 14.0 months (radium-223) vs 11.2 months (placebo); HR 0.70; 95% CI 0.55–0.88; $p < 0.001$ [23]
Sipuleucel-T	IMPACT (NCT00065442)	Placebo	Asymptomatic or minimally symptomatic mCRPC with no visceral metastases	OS, median 25.8 months (sipuleucel-T) vs 21.7 months (placebo); HR 0.78; 95% CI 0.61–0.98; $p = 0.03$ [24]
[^{177}Lu]Lu-PSMA-617 (plus BSOC[a])	VISION (NCT03511664)	Best SOC alone, including, second ARPI or glucocorticoids	PSMA-positive mCRPC with ≥1 prior ARPI and ≥1 taxane	Imaging-based PFS, median 8.7 months ([^{177}Lu]Lu-PSMA-617) vs 3.4 months (BSOC); HR 0.40; 95% CI 0.29–0.57; $p < 0.001$ [25] OS, median 15.3 months ([^{177}Lu]Lu-PSMA-617) vs 11.3 months (BSOC); HR 0.62; 95% CI 0.52–0.74; $p < 0.001$ [25]
	PSMAfore (NCT04689828)	Change of ARPI, plus best SOC	PSMA-positive mCRPC with progression after 1 prior ARPI and no prior taxane in the CRPC or mHSPC settings	Imaging-based PFS, median 12.0 months ([^{177}Lu]Lu-PSMA-617) vs 5.6 months (ARPI); HR 0.41; 95% CI 0.29–0.56; $p < 0.001$ [81, 82]
Olaparib (monotherapy or in combination with abiraterone)	PROfound (NCT02987543)	Second ARPI (abiraterone or enzalutamide)	mCRPC that is HRR-deficient; prior ARPI ± prior taxane	Imaging-based PFS (in cohort with *BRCA1*, *BRCA2*, or ATM alteration): median 7.4 months (olaparib) vs 3.6 months (ARPI); HR 0.34; 95% CI 0.25–0.47; $p < 0.001$ [58]

Table 2. continued

Drug	Clinical trial name	Comparator	Study population	Results for primary endpoint(s)
	PROpel (NCT03732820)	Placebo (with abiraterone)	mCRPC unselected by HRR status	ITT group: Imaging-based PFS: median 24.8 months (olaparib + abiraterone) vs 16.6 months (abiraterone); HR 0.66; 95% CI 0.54–0.81; $p < 0.001$ [60] OS: median 42.1 months (olaparib + abiraterone) vs 34.7 months (abiraterone); HR 0.81; 95% CI 0.67–1.00; $p = 0.054$ [26] HRR+ group: Imaging-based PFS: HR 0.50; 95% CI 0.34–0.73 OS: HR 0.66; 95% CI 0.45–0.95 [26] *BRCA* subgroup: Imaging-based PFS: HR 0.23; 95% CI 0.12–0.43 OS: HR 0.29; 95% CI 0.14–0.56 [26]
Rucaparib	TRITON-3 (NCT02975934)	Physician's choice (abiraterone, enzalutamide or docetaxel)	mCRPC that is HRR-deficient (*BRCA1/2* or *ATM* alteration only) with prior ARPI	Imaging-based PFS, *BRCA* subgroup: median 11.2 months (rucaparib) vs 6.4 months (physician's choice); HR 0.50; 95% CI 0.36–0.69 [57] ITT group: median 10.2 months (rucaparib) vs 6.4 months (physician's choice); HR 0.61; 95% CI 0.47–0.80; $p < 0.001$ for both comparisons [57]
Talazoparib (in combination with enzalutamide)	TALAPRO-2 (NCT03395197)	Placebo (with enzalutamide)	mCRPC with genetic alterations to HRR genes	Imaging-based PFS: ITT group: median not reached (talazoparib + enzalutamide) vs 21.9 months (enzalutamide); HR 0.63; 95% CI 0.51–0.78; $p < 0.001$ [28] HRR+ group: HR 0.45; 95% CI 0.33–0.61 [105] *BRCA* subgroup: HR 0.20; 95% CI 0.11–0.36 [105]
Niraparib (in combination with abiraterone)	MAGNITUDE	Placebo (with abiraterone)	mCRPC with genetic alterations to HRR genes	Imaging-based PFS, *BRCA* subgroup: median 16.6 months (niraparib + abiraterone) vs 10.9 months (abiraterone); HR 0.53; 95% CI 0.36–0.79; $p = 0.001$ [29] Overall HRR+ group, median 16.5 months (niraparib + abiraterone) vs 13.7 months (abiraterone); HR 0.73; 95% CI 0.56–0.96; $p = 0.022$ [29]
Pembrolizumab	Data pooled from five clinical trials	No comparator	Any advanced solid tumor that is MSI-H OR dMMR with no satisfactory alternative treatment options	ORR 39.6%; 95% CI 31.7–47.9% [69]

ARPI androgen receptor pathway inhibitor, *ATM* ataxia–telangiectasia mutated, *BRCA* breast cancer gene, *BSOC* best standard of care, *CRPC* castration-resistant prostate cancer, *dMMR* deficient mismatch repair, *HRR* homologous recombination repair, *HHR+* homologous recombination repair positive, *ITT* intention-to-treat, *Lu* lutetium, *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *MSI-H* microsatellite instability-high, *OR* objective response, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PSMA* prostate-specific membrane antigen.
[a]BSOC could include an ARPI in VISION but not in PSMAfore.

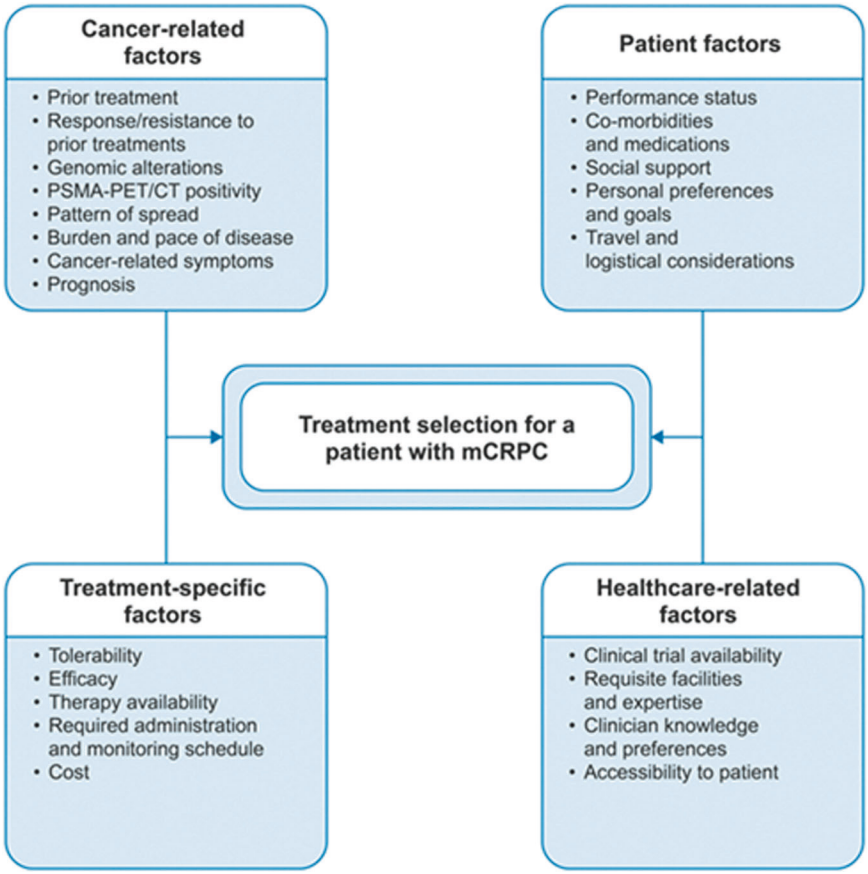


Fig. 1 Considerations during treatment selection for patients with mCRPC*. CT computed tomography, mCRPC metastatic castration-resistant prostate cancer, PET positron emission tomography, PSMA prostate-specific membrane antigen. *Please note that not all factors presented in this figure were within the scope of this review.

received SBRT [47]. The median PFS was 6.4 months (95% confidence interval [CI] 5.9–12.8 months), which exceeded the investigators hypothesized median PFS of 4 months [47]. The investigators commented that over 40% of patients remained progression-free at 12 months, and that treatment did not impact patient quality of life [47]. Several retrospective series have evaluated the outcomes of patients with oligoprogressive CRPC lesions treated with metastasis-directed therapy, demonstrating improved PFS and delays in systemic therapy change [30, 46]. In patients with limited sites of disease progression, treatment with metastasis-directed therapy can be considered to delay the need to switch systemic therapy; however, larger studies are required.

Prognosis

The pattern of metastasis in patients with mCRPC has been established as a prognostic factor [43]. In addition to visceral metastases, multiple clinical factors have demonstrated an association with varying prognoses, including PSA, alkaline phosphatase, hemoglobin, albumin, and lactate dehydrogenase [48–50]. Several multivariable models are available that incorporate these factors to help inform prognoses for patients with mCRPC [48–50], and prognostic knowledge from these models may inform treatment decision-making.

Genotypic and phenotypic testing

Approximately 11% of patients with metastatic PC may harbor a germline mutation in DNA-repair genes [51]. However, PCs can possess a somatic mutation not present in the germline [52]. In one study, ~50% of somatic mutations in homologous recombination repair (HRR) genes were also identified on germline testing [53]. Subsequently, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 4.2024 recommend both germline and somatic tumor genetic testing for all patients with metastatic PC [3]. However, real-world rates of genetic testing remain low [54]. A study assessing data from 2013 to 2019 demonstrated that only 13% (674/5213) of patients with mCRPC had undergone any genetic testing [54]. Genetic testing of patients with mCRPC should be prioritized at treatment initiation to ensure a complete assessment of potential treatment options.

Increased use of genetic testing can expand available therapy options in the mCRPC setting, including PARP and immune checkpoint inhibitors. Furthermore, early genetic testing may allow for clinical trial enrollment based on specific mutations, which could improve our understanding of individual disease biology, and also provide opportunities to identify relatives with high-risk genotypes for cancer screening. Somatic tumor testing is recommended for all patients with metastatic PC [3]. When a metastatic biopsy is not feasible, a plasma circulating tumor DNA assay can be utilized [55]. Clonal hematopoiesis of indeterminate potential, the acquisition of somatic mutations in hematopoietic cells and their clonal expansion in the absence of cancer, can be a potential source of false positives when utilizing circulating tumor DNA assays to identify tumor-derived alterations in PC [56]. Repeat testing can be considered at times of disease progression to allow the identification of targetable alterations developed later in disease evolution.

HRR gene alterations. Genetic testing can provide therapeutically actionable insights through the identification of germline or somatic mutations. PARP inhibitors, which inhibit the repair of

DNA single-stranded breaks and induce DNA double-strand breaks, are one treatment option for patients with mCRPC with a HRR gene mutation [57, 58]. In the US, two PARP inhibitors (olaparib and rucaparib) are approved as monotherapy for mCRPC in patients with HRR deficiency. Olaparib is approved for use after an ARPI, before or after docetaxel in patients with an HRR gene alteration [14]. Rucaparib is approved for patients with mCRPC harboring a *BRCA1* or *BRCA2* alteration after treatment with an ARPI and taxane-based chemotherapy [3]. The timing of treatment with PARP inhibitors, before or after taxane-based chemotherapy, should be considered in addition to HRR alterations and patient preference. In the phase 3 randomized trials PROfound (NCT02987543), and TRITON-3 (NCT02975934), treatment with PARP inhibitors was favored in both chemotherapy-naïve patients and those who had received prior taxane-based chemotherapy [57, 58]. In an exploratory analysis of a subgroup of TRITON-3 evaluating patients with *BRCA* alterations, the median PFS with rucaparib (11.2 months) was longer than with docetaxel (6.4 months; $p < 0.001$) [57]. Based on these results, PARP inhibitors represent a potential treatment option both before and after docetaxel in patients with *BRCA*-mutated (*BRCA*m) mCRPC. Additionally, while olaparib is approved for patients with a spectrum of HRR mutations, patients with *BRCA2* mutations appear to derive the greatest benefit [58]. Thus, the use of PARP inhibitors could be prioritized earlier in the treatment sequence for patients with *BRCA* mutations vs less susceptible HRR gene alterations [58].

PARP inhibitors, in combination with ARPIs, have been approved in the US for patients with mCRPC and select HRR gene mutations [14–16, 18]. However, preclinical models suggested that PARP inhibitors combined with ARPIs would have a synergistic antitumor effect irrespective of HRR alteration [59]. Thus, the phase 3 trials leading to FDA approval of these PARP inhibitor/ARPI combinations included patients with HRR mutations and patients with mCRPC irrespective of HRR mutation status [26–28, 58, 60]. In the phase 3 PROpel trial (NCT03732820), the combination of abiraterone plus olaparib as first-line treatment resulted in improved PFS compared with abiraterone plus placebo (median: 24.8 vs 16.6 months; HR 0.66; 95% CI 0.54–0.81; $p < 0.001$) irrespective of HRR status [60]. In a post hoc exploratory analysis, the radiographic PFS (rPFS) benefit of olaparib plus abiraterone was most pronounced in the HRR-mutated (HRRm) (HR 0.50; 95% CI 0.34–0.73) and *BRCA*m subgroups (HR 0.23; 95% CI 0.12–0.43) [60, 61]. The final OS analysis from PROpel demonstrated a trend toward improved OS, with a median OS of 42.1 months in patients treated with abiraterone plus olaparib vs 34.7 months in patients treated with abiraterone plus placebo (HR 0.81 95% CI 0.67–1.00, $p = 0.0544$) irrespective of HRR status [26]. In a post hoc exploratory assessment of OS, the HR was 0.66 (95% CI 0.45–0.95) in the HRRm subgroup and 0.29 (95% CI 0.14–0.56) in the *BRCA*m subgroup [26].

Similarly, in the phase 3 study TALAPRO-2 (NCT03395197), talazoparib plus enzalutamide significantly improved rPFS compared with enzalutamide plus placebo (median: not reached vs 21.9 months, respectively; HR 0.63; 95% CI 0.51–0.78; $p < 0.001$), regardless of HRR gene mutation status, as well as in the HRRm group (median: not reached vs 13.8 months, respectively, HR 0.45; 95% CI 0.33–0.61; $p < 0.001$). OS remains immature in this trial [62]. Contrastingly, in the phase 3 trial MAGNITUDE (NCT03748641), a significant rPFS benefit was seen for patients in the *HRR*m cohort treated with niraparib plus abiraterone, compared with placebo plus abiraterone for first-line mCRPC (median: 16.5 vs 13.7 months, respectively; HR 0.73; 95% CI 0.56–0.96; $p = 0.022$) but not in the non-*HRR*m cohort (HR 1.09; 95% CI 0.75–1.57; $p = 0.66$) [29]. Final OS analysis of patients with *BRCA*m mCRPC demonstrated improved OS for patients receiving niraparib plus abiraterone after pre-specified adjustment for imbalances in baseline characteristics (HR 0.66; 95% CI 0.46–0.95; $p = 0.02$) [63].

In a meta-analysis of the PROpel, TALAPRO-2, and MAGNITUDE trials investigating PARP inhibitor plus ARPI combinations vs placebo plus ARPI in first-line mCRPC, the pooled HRs were 0.62 (95% CI 0.53–0.72) for rPFS, and 0.84 (95% CI 0.72–0.98) for OS [4]. This suggests a benefit from the combination in HRR-unselected mCRPC, as PROpel and TALAPRO-2 assessed rPFS independent of HRR status [4]. At present, several PARP inhibitor/ARPI combinations are FDA-approved for select patients with HRR-altered mCRPC, including olaparib plus abiraterone and prednisone/prednisolone (*BRCA1/2*-mutated mCRPC), talazoparib plus enzalutamide (HRRm mCRPC), and niraparib plus abiraterone and prednisone (*BRCA*m mCRPC) [14, 16, 18]. Of note, the FDA and European Medicines Agency (EMA) labels for the combinations of olaparib plus abiraterone and talazoparib plus enzalutamide differ. In the US, the combination of olaparib or niraparib plus abiraterone and prednisone/prednisolone is approved for adult patients with mCRPC and deleterious or suspected deleterious *BRCA* mutations, whereas talazoparib plus enzalutamide is approved for adult patients with mCRPC and select HRR mutations (*BRCA1*, *BRCA2*, *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, and *RAD51C*) [14, 16]. Contrastingly, the EMA labels for both combinations of olaparib plus abiraterone and prednisone/prednisolone, and talazoparib plus enzalutamide, include patients with mCRPC for whom chemotherapy is not clinically indicated, regardless of *HRR*m status [64, 65]. When choosing between the available combinations, multiple factors, including specific mutations, toxicity differences (e.g., rates of grade ≥3 anemia), data maturity (PROpel is the only study with OS benefit demonstrated to date), and accessibility should be considered [26, 28, 60, 63]. Of note, patients with mCRPC who developed resistance on a prior ARPI were not represented in PROpel, MAGNITUDE, or TALAPRO-2, so the benefit of these combinations in these patients is not known [28, 60, 63].

Individual HRR gene mutations demonstrate heterogeneous sensitivity to PARP inhibitors. In an exploratory pooled analysis from the FDA including three PARP inhibitor plus ARPI trials and three PARP inhibitor monotherapy trials in patients with mCRPC, the benefit of PARP inhibitor treatment appeared greatest for patients with *BRCA1 and BRCA2* mutations as well as *CDK12 and PALB2* mutations, with a lack of treatment effect demonstrated in patients with *CHEK2* or *ATM* mutations in these studies [66].

MSI-H/dMMR or TMB-high. Deficient mismatch repair (dMMR) prevents the reversal of DNA base mismatches that may occur during cellular replication, resulting in high microsatellite instability (MSI-H) and a hypermutator phenotype associated with chemotherapy resistance and immunotherapy sensitivity [67]. Although dMMR and MSI-H are relatively uncommon in PC (<9%), they can be therapeutically meaningful for patients [67, 68]. Pembrolizumab, an anti-programmed cell death protein-1 (PD-1) antibody, is a treatment option for patients whose tumors have dMMR/MSI-H or a high tumor mutational burden (TMB-H) [≥10 mutations/megabase] [3]. Pembrolizumab received tumor-agnostic FDA approval for the treatment of advanced solid tumors (including PC) that are MSI-H/dMMR or TMB-H when there are no satisfactory alternative treatments [69]. However, data remain limited to small retrospective trials [31, 68]. In a retrospective case series of 11 patients with MSI-H/dMMR CRPC receiving anti-PD-1/programmed death-ligand 1 therapy, 6 (54.5%) patients had a ≥50% PSA decline, and 4 (36.4%) demonstrated radiographic responses [68]. In another retrospective series of 27 patients with dMMR/MSI-H metastatic PC, 8/17 (53.0%) pembrolizumab-treated patients experienced PSA responses ≥50%, of whom 7 (87.5%) remained on treatment without progression at 12 months median follow-up (range: 3–20 months) [31]. Therefore, treatment with pembrolizumab can be considered prior to docetaxel for patients with dMMR/MSI-H or TMB-H mCRPC, generally after an ARPI. Dostarlimab, another anti-PD-1 antibody, has histology-agnostic FDA approval for dMMR tumors; however, data are limited in patients with PC [70].

PSMA-positive disease. For patients with PSMA-positive metastatic disease who received prior treatment with ≥1 ARPI and

taxane-based chemotherapy, treatment with the PSMA-targeted radioligand therapy (RLT) [^{177}Lu]Lu-PSMA-617 is an option [13]. Patients must undergo PSMA PET imaging to assess eligibility, including ≥1 PSMA-positive metastatic lesion and no PSMA-negative lesions [3, 13]. [^{68}Ga]Ga-PSMA-11 is currently the only radiopharmaceutical approved by the FDA to assess eligibility for [^{177}Lu]Lu-PSMA-617 treatment; however, according to NCCN Guidelines®, PSMA PET imaging can also be performed using [^{18}F]F-DCFPyL, or [^{18}F]F-rhPSMA-7.3 [3]. In the phase 3 VISION trial (NCT03511664), treatment with [^{177}Lu]Lu-PSMA-617 plus best SOC (BSOC) prolonged rPFS and OS in patients with PSMA-positive mCRPC who had previously received ≥1 ARPI and 1–2 taxane-based chemotherapy regimens [25]. In the randomized phase 2 TheraP trial (NCT03392428) treatment with [^{177}Lu]Lu-PSMA-617 compared with cabazitaxel had fewer grade ≥3 adverse events, improved patient-reported outcomes, and yielded similar OS benefit, which may support the use of [^{177}Lu]Lu-PSMA-617 prior to cabazitaxel [71]. [^{177}Lu]Lu-PSMA-617 can also be considered after docetaxel and cabazitaxel, as [^{177}Lu]Lu-PSMA-617 demonstrated efficacy in patients who had received 1–2 taxane-based chemotherapy regimens in the VISION trial [25].

There is emerging evidence that higher baseline levels of uptake (standardized uptake value mean [SUV_{mean}]) and lack of liver metastases on PSMA PET correlate with improved outcomes following treatment with [^{177}Lu]Lu-PSMA-617 [72]. However, treatment with [^{177}Lu]Lu-PSMA-617 plus BSOC prolonged rPFS and OS in patients with PSMA-positive mCRPC, inclusive of eligible patients with lower SUV_{mean} [25]. Additional evidence is required to validate this association before these measures can be applied in clinical practice [72]. Some patients will have PSMA-negative disease and will not be candidates for PSMA-targeted therapy; in the VISION trial, 12.6% of patients did not meet eligibility criteria based on PSMA imaging [25]. In the updated survival analysis of TheraP, no OS differences were observed between [^{177}Lu]Lu-PSMA-617 and cabazitaxel (19.1 vs 19.6 months, respectively) irrespective of baseline PSMA PET SUV_{mean}, and patients with high SUV_{mean} (>10) had improved outcomes irrespective of therapy [73], suggesting that PSMA SUV_{mean} is prognostic and not predictive, and that the outcomes of mCRPC patients are similar regardless of [^{177}Lu]Lu-PSMA-617 or taxane-based chemotherapy treatment sequencing.

Tumor-agnostic drugs. In addition to the tumor-agnostic approvals for pembrolizumab and dostarlimab, several additional treatments have FDA approvals for histology-agnostic indications, including larotrectinib and entrectinib (for tumors harboring neurotrophic tyrosine receptor kinase [*NTRK*] fusions), dabrafenib plus trametinib (for *BRAF* V600E-mutated tumors), and selpercatinib (for rearrangements during transfection [*RET*] gene fusions) [74–77]. Experience with these agents in PC is limited outside of pembrolizumab.

Patient-specific factors and preferences

Patient-specific factors, including co-morbidities and performance status, are important considerations for treatment selection. Frail patients with multiple co-morbidities may not be candidates for taxane-based chemotherapy but could receive therapies associated with lower adverse event incidences [78, 79]. Alternative dosing strategies, which improve tolerability while preserving efficacy, can be considered for both docetaxel and cabazitaxel in this population [78, 79]. Individual circumstances (e.g., the ability to travel) and cost may influence access and feasibility of certain treatments. Importantly, patient goals and preferences should be key considerations during treatment selection. Establishing an understanding of the risk tolerance and priorities of patients and their caregivers can also aid decision-making.

Clinic-related factors

Factors regarding the clinical setting in which patients are treated influence therapy selection. When available, clinical trials should be considered for all patients with mCRPC [3], but the availability of suitable trials varies depending on treatment setting. An oncology provider's specialty, and ability to collaborate in multidisciplinary care, may influence therapy availability. Clinic-specific logistical considerations (e.g., availability of specific facilities) and reimbursement issues also influence treatment decisions. Utilization and timing of radiopharmaceuticals may be influenced by access to a center with the required infrastructure, multidisciplinary teams, and investment to provide these therapies.

Often, there is no definitive optimal treatment option for a patient with mCRPC. Reaching a therapeutic decision requires consideration of many factors and thoughtful discussion with patients regarding their options. The general principles reviewed above are summarized in Fig. 2 and can be used as a framework to guide decision-making.

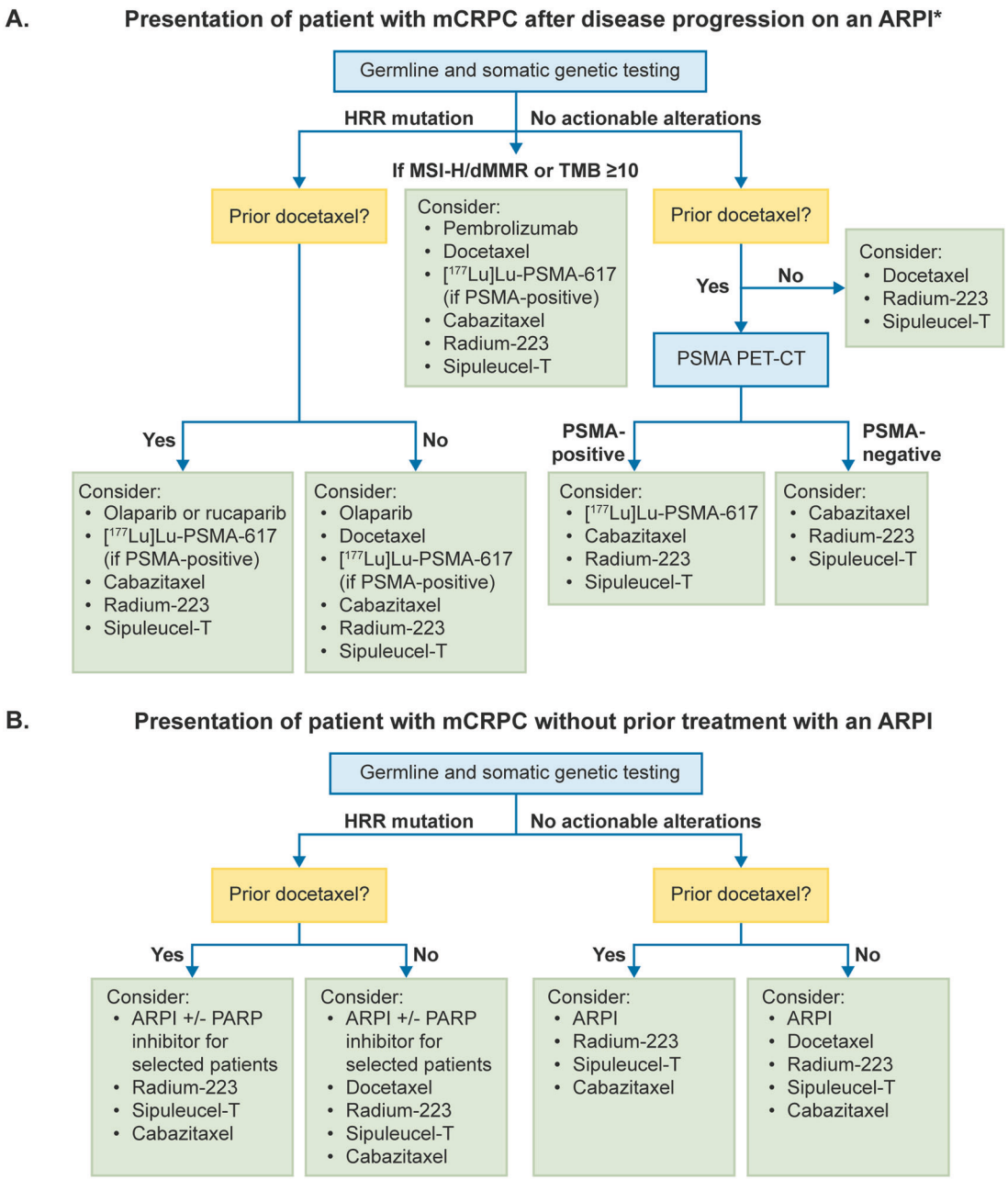
FUTURE THERAPEUTIC STRATEGIES

New therapeutic strategies in the treatment of mCRPC are currently being investigated. New therapeutic options will become available as results are published, further changing the sequencing of therapies. Use of PSMA-targeted RLT, such as [^{177}Lu]Lu-PSMA-617, earlier and in combinations, is a key focus of ongoing trials.

PSMA-targeted RLT

Interest in [^{177}Lu]Lu-PSMA-617 has increased following its approval for the treatment of patients with PSMA-positive mCRPC post-treatment with ARPI and taxane-based chemotherapy [13]. As patients may now receive treatment with an ARPI and taxane-based chemotherapy in the mHSPC setting [3], [^{177}Lu]Lu-PSMA-617 is increasingly being used as a first-line treatment for mCRPC [25, 80]. Earlier use of [^{177}Lu]Lu-PSMA-617 in patients with PSMA-positive mCRPC is being evaluated in the phase 3 PSMAfore (NCT04689828) trial in patients who have not received taxane-based chemotherapy [81, 82]. PSMAfore met its primary endpoint, demonstrating significantly improved rPFS in patients randomized to [^{177}Lu]Lu-PSMA-617 vs an ARPI change (HR 0.41; 95% CI 0.29–0.56; $p < 0.0001$), in addition to improved ORR ([^{177}Lu]Lu-PSMA-617 vs ARPI change: 50.7% vs 14.9%) and time to worsening of health-related quality of life (FACT-P total score, HR 0.59; 95% CI 0.47–0.72) [81, 82]. At the third interim OS analysis (with 73% of targeted events), the pre-specified crossover-adjusted OS analysis demonstrated a HR of 0.98 (95% CI 0.76–1.27) [83]. Unadjusted intention-to-treat OS analysis demonstrated a HR of 0.98 (95% CI 0.75–1.28) but was confounded by 78% crossover after progression on ARPI change [83]. Significant delays in time to worsening in health-related quality of life and pain were observed with PSMA RLT vs ARPI change at second interim OS analysis [83]. These data support the efficacy of PSMA-RLT in patients with mCRPC prior to docetaxel therapy, following progression on an ARPI. The value of PSMA-RLT in addition to an ARPI was assessed in the ENZA-p (NCT04419402) trial, which demonstrated significantly improved PSA-based outcomes in high-risk, first-line mCRPC vs enzalutamide alone, suggesting future larger studies should evaluate combination approaches [84]. The PSMAddition (NCT04720157) trial is assessing the efficacy and safety of [^{177}Lu]Lu-PSMA-617 in combination with ARPI in patients with mHSPC [85].

Although [^{177}Lu]Lu-PSMA-617 is currently the only FDA-approved PSMA-targeted RLT, other strategies are under investigation, including [^{177}Lu]Lu-PNT2022, I-131-1095 (small-molecule PSMA-targeted ^{131}I-based RLT) and strategies utilizing alpha-emitters (e.g., actinium-225; [^{225}Ac]Ac-J591) [86, 87]. [^{177}Lu]Lu-PNT2022 is being investigated in two phase 3 trials, SPLASH (NCT04647526) and ECLIPSE (NCT05204927), comparing it with abiraterone or enzalutamide in patients with mCRPC who have received one prior ARPI and no prior chemotherapy [88, 89]. No data from these trials have been published, aside from the results of a 27-patient lead-in phase from



General principles of treatment selection:

- Re-consult treatment selection algorithm for each new line of therapy.
- Continue ADT regardless of changes in therapy.
- Genetic testing (germline and somatic) should be performed at diagnosis of mCRPC (if not previously) for all patients.
- Prioritize therapies with a new mechanism of action after disease progression on a prior agent.
- Radium-223: only for patients with symptomatic bone metastases and no visceral metastases.
- Sipuleucel-T: only for patients with asymptomatic or minimally symptomatic disease and no visceral metastases; consider only when disease burden is limited.
- Patients with bone metastases should receive concurrent bone-modifying agents.
- All treatment decisions made with consideration of patient goals and preferences.

Fig. 2 Treatment selection algorithms for mCRPC. A Treatment selection algorithm for mCRPC in patients with progressive disease following treatment with an ARPI. **B** Treatment selection algorithm for mCRPC in patients without prior ARPI. ADT androgen deprivation therapy, ARPI androgen receptor pathway inhibitor, CRPC castration-resistant prostate cancer, CT computed tomography, HRR homologous recombination repair, Lu lutetium, mCRPC metastatic castration-resistant prostate cancer, MSI-H microsatellite instability-high, PARP poly (ADP-ribose) polymerase, PET positron emission tomography, PSMA prostate-specific membrane antigen, TMB tumor mutational burden. *If aggressive mCRPC disease features (e.g., liver metastases, short time to CRPC, multiple lytic bone lesions), prioritize taxane chemotherapy (consider adding carboplatin) if a candidate.

SPLASH [88, 89]. I-131-1095 radiotherapy (in combination with enzalutamide) is being evaluated in the randomized phase 2 ARROW trial (NCT03939689), comparing it with enzalutamide in patients with mCRPC who experienced disease progression on abiraterone; no data have been published [87].

Multiple ongoing trials are investigating PSMA-RLT in combination with other therapies for mCRPC, with the goal of improving disease control [86, 90, 91]. [^{177}Lu]Lu-PSMA-617 is being assessed in combination with: olaparib (NCT03874884), cabazitaxel (NCT05340374), ipilimumab plus nivolumab (NCT05150236), pembrolizumab (NCT03658447 and NCT05766371), abemaciclib (NCT05113537), and cabozantinib (NCT05613894), while [^{177}Lu]Lu-PSMA-I&T is being assessed in combination with radium-223 (NCT05383079) [86, 90, 91].

Evidence gaps and future directions

Despite numerous therapeutic strategies, evidence gaps regarding optimal treatment selection remain. These are particularly substantial in the post-ARPI space, as pivotal trials of many current treatments were performed in patients who had not received a prior ARPI [22, 23, 30, 92]. Additionally, pivotal trials of current treatments utilized conventional imaging to determine metastatic disease [22, 23, 30, 92]. The use of more sensitive PSMA PET imaging, now routine in clinical practice, may identify metastases in patients that previously would have been classified as having M0 CRPC with conventional imaging [93]. This earlier detection of mCRPC may allow treatment earlier in the disease course.

Novel agents with different MoAs, including androgen receptor degraders, and immunotherapeutic strategies, such as bispecific T-cell engagers and chimeric antigen receptor T-cell therapies [94], are being evaluated in phase 1/2 trials. With the exception of PD-1 blockade in patients with mCRPC harboring MSI-H/dMMR or TMB-H tumors, PD-1 blockade in PC has provided limited survival benefit, and ongoing strategies to understand immune evasion and increase the effectiveness of checkpoint blockade in mCRPC are needed [31, 68]. The combination of cabozantinib, a small-molecule receptor tyrosine kinase inhibitor, plus atezolizumab, an anti-PD-L1 antibody, is being studied in the phase 3 CONTACT-02 trial, demonstrating a statistically significant improvement in PFS compared with a second ARPI at the primary analysis [95].

Predictive biomarkers and the development of clinical–genomic models to help guide optimal therapy selection represent key future study areas. Biomarkers of poor outcomes and ARPI resistance, including aggressive variant signatures (e.g., PTEN), and biomarkers predictive of improved outcomes with ARPI treatment (e.g., SPOP) are emerging and may soon become actionable [96, 97]. Understanding mechanisms of resistance to androgen receptor signaling inhibition, and how to target these pathways, are important areas for ongoing discovery [98]. While not covered here, PC with neuroendocrine/small cell features represents an important area of needed investigation and additional treatment options.

It is important to note that this review focuses on practice patterns in the US, which is a limitation of this article. Further work that describes different treatment sequences globally is needed, given the variation in practice patterns between different countries and regions [99].

CONCLUSION

Our understanding of mCRPC has improved dramatically due to advances in genetic testing, molecular imaging, and further evidence-based learnings. Consequently, multiple treatment options now exist for mCRPC, contributing to improved prognoses for patients. However, these new developments make individual treatment decision-making more complex, thus uncertainties regarding optimal treatment choices and sequencing in clinical practice remain. Continued multidisciplinary collaboration and attention to regular educational updates are important.

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AUTHOR CONTRIBUTIONS

HDM was responsible for the conception, design, and execution of the study, interpreting the data, drafting the paper, revising the paper critically for intellectual content, and providing final approval of the final draft for publication. TD was responsible for the conception, design, and execution of the study, interpreting the

data, drafting the paper, revising the paper critically for intellectual content, and providing final approval of the final draft for publication. AKM was responsible for the conception, design, and execution of the study, interpreting the data, drafting the paper, revising the paper critically for intellectual content, and providing final approval of the final draft for publication. OS was responsible for the conception, design, and execution of the study, interpreting the data, drafting the paper, revising the paper critically for intellectual content, and providing final approval of the final draft for publication. NS was responsible for the conception, design, and execution of the study, interpreting the data, drafting the paper, revising the paper critically for intellectual content, and providing final approval of the final draft for publication. AJA was responsible for the conception, design, and execution of the study, interpreting the data, drafting the paper, revising the paper critically for intellectual content, and providing final approval of the final draft for publication.

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