Systemic treatment options for metastatic castration resistant prostate cancer: A living systematic review.

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Abstract

Background: Optimal treatment selection for metastatic castration resistant prostate cancer (mCRPC) remains challenging due to evolving standards of care in castration sensitive setting.

Purpose: To synthesize and appraise evidence on systemic therapy for mCRPC patients stratified by prior therapy and *HRR* alterations informing a clinical practice guideline.

Data Sources: MEDLINE and EMBASE (inception to 5 March 2025) using living search.

Study Selection: Randomized clinical trials assessing systemic therapy in mCRPC.

Data Extraction: Primary outcomes assessed were progression free survival (PFS) and overall survival (OS).

Data Synthesis: This report of the living systematic review (LSR) includes 143 trials with 17,523 patients (59 phase III/IV trials, 8,941 patients; 84 phase II, 8,582 patients). In the setting of prior androgen deprivation therapy (ADT) alone or ADT+docetaxel, treatment benefit was observed with poly (ADP-ribose) polymerase inhibitors (PARPi) in combination with androgen receptor pathway inhibitors (ARPI) for *BRCA*+ subgroup. In the setting of prior ADT+ARPI or ADT+ARPI+docetaxel, treatment benefit was observed with PARPi monotherapy for *BRCA*+ subgroup. Treatment benefit with PARPi may be observed for select non-*BRCA* homologous recombination repair (*HRR*) alterations (*CDK12*, *PALB2*). Treatment benefit was observed with abiraterone, enzalutamide, cabazitaxel, docetaxel (if no prior docetaxel), and Lu^{177} (if PSMA+) for patients without *HRR* alterations.

Limitations: Study-level data and indirectness in evidence.

Conclusion: Findings from the current LSR suggest that optimal treatment for mCRPC should be individualized based on prior therapy and *HRR* alterations. Current evidence favors PARPi

alone (ARPI exposed) or in combination with ARPI (ARPI naïve) for patients with *BRCA* alterations, while ARPI alone, chemotherapy, and Lu^{177} remain potential options for patients without *HRR* alterations.

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Introduction

Metastatic castration resistant prostate cancer (mCRPC) is a lethal disease with a median survival of 25.6 months [1]. It has been an area of active investigation with hundreds of trials conducted over the last decade. Several agents such as androgen receptor pathway inhibitors (ARPI), novel chemotherapeutics, poly (ADP-ribose) polymerase (PARP) inhibitors, and radiopharmaceutical therapies have been approved. While this pace of drug approvals is a blessing, it also becomes challenging to reconcile evidence from trials over the last decades for current clinical practice due to factors such as evolving standard of care in metastatic hormone sensitive prostate cancer (mHSPC), heterogeneous inclusion criteria related to prior lines of treatment, control arms that do not always reflect clinical practice, and the need to consider clinically relevant subgroups defined by homologous recombination repair (*HRR*) pathway alterations, and prostate-specific membrane antigen (PSMA) expression.

Here, we have developed a living systematic review (LSR) to support the rapidly evolving clinical practice guidelines for the management of mCRPC. The goal of this systematic review is to summarize evidence from all randomized clinical trials and present it with emphasis on the following key points (1) evidence for each drug class and drug type as a quick resource for evidence repository in mCRPC (2) evidence by receipt of previous treatment to contextualize the evidence in relevance to clinical practice (3) and evidence stratified by different alterations in the *HRR* pathway. This LSR will be continuously updated as new evidence is published, and the updates will be hosted on a companion interactive website (**living website link**). By facilitating ongoing

updates and interactive components, this review seeks to provide a comprehensive and dynamic resource that adapts to the evolving landscape of mCRPC management.

Methods

This LSR was conducted using the living interactive evidence (LIvE) synthesis framework [2-4] and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [5] (**Supplement Methods 1**). This study was registered in the Open Science Framework (https://osf.io/46tjm).

Data Sources and Search

MEDLINE and EMBASE were comprehensively searched using a structured search strategy (**Supplement Methods 2**). Subsequently, a "living" auto search has been created with weekly updates to identify new evidence as it becomes available. The cutoff date for this report from our LSR is March 5th, 2025.

Study Selection

Full-text articles of phase II, III or IV randomized clinical trials assessing systemic therapy in mCRPC were included. Trials before 1990, purely phase I trials, articles in non-English language, and non-randomized studies were excluded.

Study selection was conducted by two independent reviewers (SAAN and UA) with discrepancies resolved by the senior reviewer (IBR).

Data Extraction and Quality Assessment

The extracted data included trial characteristics, baseline population characteristics, outcome results in the overall population and in clinically relevant subgroups. Two reviewers (SAAN and UA) independently extracted data with machine-facilitated annotations and examined risk of bias using the Cochrane Risk of Bias tool

version 2 [6]. Discrepancies were resolved by consensus and input from a third reviewer (IBR).

Patient important outcomes included progression free survival (PFS) and overall survival (OS). In instances where multiple PFS definitions were reported, radiographic PFS (rPFS) was used (**Supplement Tables 1-2)**. Time to disease progression (TTP) or composite endpoint of PFS (defined as composite of radiographic disease progression, PSA progression and/or clinical progression) were used if PFS was not reported.

Data synthesis

The evidence was collated and stratified by (i) treatment class; (ii) treatment agent; (iii) receipt of previous treatment and (iv) *HRR* alteration status.

Eligible prior therapies included androgen deprivation therapy (ADT) with or without first-generation anti-androgens; ADT+ARPI; ADT+docetaxel; and ADT+ARPI+docetaxel. Five clinically relevant categories were defined according to the following criteria: (a) trials in which patients only received prior ADT or <25% patients received prior ARPI or docetaxel were classified into the “prior ADT” subgroup; (b) trials in which all patients received prior ADT and >75% patients received prior ARPI were classified into the “prior ADT+ARPI” subgroup; (c) trials in which all patients received prior ADT and >75% patients received prior docetaxel were classified into the “prior ADT+docetaxel” subgroup; (d) trials in which all patients received prior ADT and >75% patients received both prior ARPI and docetaxel were classified into the “prior ADT+ARPI+docetaxel” subgroup; (e) trials in which all patients received prior ADT and >25% but <75% patients received prior ARPI or docetaxel were classified into the

"heterogeneous prior therapy" subgroup. Trials were included if they met the pre-specified criteria or reported survival data by prior therapy subgroup. These criteria were finalized after consensus of a panel of oncologists.

The relative effect estimates along with their 95% confidence intervals (CI) pushed from the analysis module to the *Tabulator* module are translated into intervention risk, and absolute risk differences using relative estimates and assumed baseline event risk.

The absolute risk difference per 1000 patients using relative risk (RR) is calculated as:

$$ARD = 1000 \times baseline\ risk \times (RR - 1)$$

The absolute risk difference per 1000 patients using hazard ratio (HR) is calculated as:

$$RR = \frac{(1 - e^{HR \times \ln(1 - baseline\ risk)})}{baseline\ risk}$$

$$ARD = 1000 \times baseline\ risk \times (RR - 1)$$

Role of funding source

The funding source was not involved in the conduct of this study, interpretation of results, or preparation of this manuscript for publication.

Results

Baseline characteristics

As of March 5th 2025, 143 trials (186 references) [7-192] with 17,523 patients were included **(Figure 1)**. Of these, 84 (59%) were phase II randomized, and 59 (41%) were phase III/IV randomized clinical trials. A total of 8,582 and 8,941 patients were included in the 84 phase II [99-105,107-115,117-137,139-147,149-158,160-185,190,192], and 59 phase III/IV [7-9,11,13,15-20,26,29-38,42,45-56,58,60,65,71-78,80,84,86,87,89-91,93-95,97,186,191] trials, respectively. The median age ranged from 68 to 71 years (interquartile range) across the phase II trials, and 69 to 71 years (interquartile range) across the phase III/IV trials. Out of the 59 included phase III/IV trials, chemotherapy as monotherapy was assessed in 11 trials, ARPI monotherapy in seven trials, immunotherapy in four trials, the combination of two ARPIs in three trials, PARPi with ARPI in three trials, and radiopharmaceutical/radioligand monotherapy was assessed in two trials.

In terms of risk of bias (**Supplement Figures 1-2**), some concerns for the assessment of PFS were present in most phase II and a few phase III/IV trials due to their open-label nature. However, the risk of bias across most phase II and III/IV trials assessing OS was low.

Additional characteristics and distribution by race/ethnicity are provided in **Tables 1-6**, **Supplement Tables 3-12**, and **Supplement Results**.

Heterogeneity in reporting of outcomes and subgroups in the included trials is outlined in **Supplement Results**, and **Supplement Tables 13-16**.

Results for survival outcomes

Interactive results are available on the living website (**living website link**). Results can be conditionally filtered by treatment class, treatment type (combination vs. monotherapy), treatment agent, control, and prior therapy.

Here, we report the results for PFS and OS at the level of each phase III/IV trial organized by receipt of eligible prior therapy (**Tables 1-6** and **Supplement Table 17**). Additional results from phase II trials are provided in **Supplement Tables 6** and **18**.

(1) Prior ADT with and without first-generation anti-androgens

A total of 29 phase III trials [7,11,16-18,26,27,29,30,32-34,36,37,45-47,52-54,57,58,65,69,73,76,77,80,89,93,94,188,189] reporting PFS and 38 [7,11,13,15-18,28-30,32-34,36,37,45-49,51-54,57,58,69,72,73,75-78,80,85,89,93,94,188,189] reporting OS were considered eligible for prior ADT subgroup.

a. Monotherapy:

In terms of **ARPI monotherapy**, abiraterone acetate (COU-AA-302) was associated with a statistically significant improvement in rPFS [27] (0.52; 0.45-0.61) and OS [28] (HR: 0.81; 95% CI: 0.70-0.93) compared to placebo. Enzalutamide (PREVAIL) [57] was associated with a statistically significant improvement in rPFS (0.32; 0.28-0.36) and OS (0.77; 0.67-0.88) compared to placebo.

In terms of **chemotherapy monotherapy**, docetaxel with prednisone (TAX327) [85] was associated with a statistically significant improvement in OS (0.79; 0.67-0.93) compared to mitoxantrone with prednisone.

In terms of **single-agent immunotherapy**, sipuleucel-T was associated with a statistically significant improvement in OS compared to placebo in D9901 [29] (0.58; 0.39-0.88) but not in D9902A [93] (0.79; 0.48-1.28) and IMPACT [36] (0.79; 0.59-1.03).

In terms of **radiopharmaceutical monotherapy**, radium-223 (ALSYMPCA) [13] was associated with a statistically significant improvement in OS compared to placebo (0.69; 0.52-0.92) in docetaxel-naïve patients.

b. Combination therapy:

In terms of **combination of two ARPIs**, enzalutamide+abiraterone (Alliance A031201) [11] compared to enzalutamide alone was associated with a statistically significant improvement in rPFS (0.86; 0.76-0.97) but not in OS (0.89; 0.78-1.01).

In terms of **combination of ARPI with PARPi**, olaparib+abiraterone (PROpel) [69] was associated with a statistically significant improvement in rPFS (0.62; 0.49-0.79) but not in OS (0.85; 0.67-1.07) compared to abiraterone alone in overall population. Talazoparib combined with enzalutamide (TALAPRO-2) [189] was associated with a statistically significant improvement in both rPFS (0.67; 0.55-0.81) and OS (0.80; 0.66-0.96) compared to enzalutamide alone.

In patients with *HRR* alterations, olaparib+abiraterone (PROpel) [65,69] was associated with a statistically significant improvement in both rPFS (0.45; 0.31-0.65) and OS (0.66; 0.45-0.95). Talazoparib combined with enzalutamide (TALAPRO-2) [188] was associated with a statistically significant improvement in both rPFS (0.47; 0.36-0.61) and OS (0.62; 0.48-0.81) compared to enzalutamide alone in patients with *HRR* alterations.

In patients with *BRCA* alterations, olaparib+abiraterone (PROpel) [65,69] was associated with a statistically significant improvement in both rPFS (0.18; 0.09-0.34) and OS (0.29; 0.14-0.56) compared to abiraterone alone. Talazoparib combined with enzalutamide (TALAPRO-2) [81,188] was associated with a statistically significant improvement in both rPFS (0.20; 0.11-0.36) and OS (0.50; 0.32-0.78) compared to enzalutamide alone in patients with *BRCA* alterations.

In patients with non-*BRCA* alterations, olaparib+abiraterone (PROpel) [65,69] was associated with a statistically significant improvement in rPFS (0.72; 0.58-0.90) but not in OS (0.91; 0.73-1.13) compared to abiraterone alone. Talazoparib combined with enzalutamide (TALAPRO-2) [81,188] was associated with a statistically significant improvement in rPFS (0.71; 0.52-0.96) but not in OS (0.73; 0.52-1.02) compared to enzalutamide alone.

Results for other mono-therapeutic agents and combination therapies in patients who received prior ADT are available in **Tables 1** and **6.** Summary of findings with certainty of evidence is outlined in **Supplement Tables 19** and **24.**

(2) Prior ADT+ARPI

A total of eight [35,42,55,60,86,97,186,191] phase III/IV trials reporting PFS and five [35,61,86,97,191] reporting OS were considered eligible for prior ADT+ARPI subgroup.

a. Monotherapy:

In terms of **PARPi monotherapy**, analysis for the overall population (cohort A+B) showed that olaparib (PROfound) [60,61] was associated with a statistically significant

improvement in rPFS (0.49; 0.38-0.63) but not in OS (0.79; 0.61-1.03) compared to enzalutamide/abiraterone.

In patients with *BRCA* alterations, olaparib (PROfound) [64] was associated with a statistically significant improvement in both rPFS (0.22; 0.15-0.32) and OS (0.63; 0.42-0.95) compared to enzalutamide/abiraterone. However, subgroup analysis for patients who had received prior ARPI showed that olaparib was not associated with a statistically significant improvement in both rPFS (0.77; 0.50-1.22) and OS (1.12; 0.69-1.85) compared to enzalutamide/abiraterone. Likewise, analysis for overall population (*BRCA* and/or *ATM* alterations) showed that rucaparib (TRITON-3) [86] was not associated with a statistically significant improvement in OS (0.94; 0.72-1.23) when compared to enzalutamide/abiraterone/docetaxel. However, rucaparib was associated with a statistically significant improvement in rPFS when compared to enzalutamide/abiraterone/docetaxel (0.61; 0.47-0.80), enzalutamide/abiraterone (0.47; 0.34-0.66) and docetaxel (0.64; 0.46-0.88) in overall population (*BRCA* and/or *ATM* alterations). Results for patients with only *BRCA* alterations were also consistent.

In terms of **radioligand monotherapy**, ^{177}Lu-PSMA-617 (PSMAfore) [97] was associated with a statistically significant improvement in rPFS (0.49; 0.39-0.61) but not in OS (0.98; 0.75-1.28) compared to enzalutamide/abiraterone.

b. Combination therapy:

In terms of **addition of chemotherapy to ARPI continuation**, docetaxel+enzalutamide continuation after progression (PRESIDE) [55] was associated

with a statistically significant improvement in cPFS (0.72; 0.53-0.96) compared to enzalutamide continuation alone.

In terms of **combination of ARPI with immunotherapy**, enzalutamide+atezolizumab (IMbassador250) [35] was not associated with statistically significant rPFS improvement (0.98; 0.75-1.27) but was associated with statistically significant OS harm (1.58; 1.13-2.20) compared to enzalutamide alone.

Results for other mono-therapeutic agents and combination therapies in patients who received prior ADT+ARPI are available in **Tables 2** and **6.** Summary of findings with certainty of evidence is outlined in **Supplement Tables 20** and **24.**

(3) Prior ADT+docetaxel

A total of 9 phase III trials [9,23,31,42,50,69,71,74,87] reporting PFS and 11 [8,9,13,23,31,36,50,69,71,75,87] reporting OS were considered eligible for prior ADT+docetaxel subgroup.

a. Monotherapy:

In terms of **ARPI monotherapy**, abiraterone (COU-AA-301) [23] was associated with a statistically significant improvement in both rPFS (0.66; 0.58-0.76) and OS (0.74; 0.64-0.86) compared to placebo. Enzalutamide (AFFIRM) [9] was associated with a statistically significant improvement in both rPFS (0.40; 0.35-0.47) and OS (0.63; 0.53-0.75) compared to placebo.

In terms of **chemotherapy monotherapy**, cabazitaxel 25 mg/m² (TROPIC) [87] was associated with a statistically significant improvement in both cPFS (0.74; 0.64-0.86) and OS (0.70; 0.59-0.83) compared to mitoxantrone.

In terms of **radiopharmaceutical monotherapy**, radium-223 (ALSYMPCA) [13] was associated with a statistically significant improvement in OS (0.70; 0.56-0.88) compared to placebo in patients who received prior docetaxel.

b. Combination therapy:

In terms of **combinations of ARPI with PARPi,** niraparib combined with abiraterone (MAGNITUDE) [42] was not associated with a statistically significant improvement in rPFS (0.89; 0.48-1.66) compared to abiraterone alone in overall population. In patients with *HRR* alterations, niraparib + abiraterone was associated with a statistically significant improvement in both rPFS (0.76; 0.60-0.97) and OS (0.70; 0.49-0.99) after adjusting for cross-over. In patients with *BRCA* alterations, niraparib + abiraterone (MAGNITUDE) [42,43] was associated with a statistically significant improvement in both rPFS (0.55; 0.39-0.78) and OS (0.54; 0.33-0.90) after adjusting for cross-over, compared to abiraterone alone.

In patients with non-*BRCA* alterations, niraparib+abiraterone (MAGNITUDE) [42] was not associated with a statistically significant improvement in rPFS (0.99; 0.68-1.45) compared to abiraterone alone. OS was not reported.

Results for other mono-therapeutic agents and combination therapies in patients who received prior ADT+docetaxel are available in **Tables 3** and **6.** Summary of findings with certainty of evidence is outlined in **Supplement Tables 21** and **24.**

(4) Prior ADT+ARPI+docetaxel

A total of four phase III/IV trials reporting PFS [19,38,91,95] and OS [19,38,91,95] were considered eligible for prior ADT+ARPI+docetaxel subgroup. These trials included patients who had progressed on/previously received both ARPI and docetaxel separately but not in combination with intent of triplet therapy in mHSPC setting.

In terms of **chemotherapy monotherapy**, cabazitaxel 25 mg/m² (CARD) [95] was associated with a statistically significant improvement in both rPFS (0.54; 0.40-0.73) and OS (0.64; 0.46-0.89) compared to enzalutamide/abiraterone.

In terms of **radioligand therapy**,^{177}Lu-PSMA-617 added to standard of care (VISION) in PSMA-positive patients [91] was associated with a statistically significant improvement in both rPFS (0.40; 0.29-0.57) and OS (0.62; 0.52-0.74) compared to standard of care.

In terms of **TKI monotherapy**, cabozantinib (COMET-1) [19] was associated with a statistically significant improvement in rPFS (0.48; 0.40-0.57) but not in OS (0.90; 0.76-1.06) compared to prednisone.

Results for other combination therapies in patients who received prior ADT+ARPI+docetaxel are available in **Table 4.** Summary of findings with certainty of evidence is outlined in **Supplement Table 22** and **24.**

Results for mono-therapeutic agents and combination therapies in patients who received heterogeneous prior therapy are available in **Tables 5** and **6.** Summary of findings with certainty of evidence is outlined in **Supplement Tables 23-24.**

Discussion

This report from the living, interactive systematic review presents comprehensively synthesized and critically appraised relative and absolute effects of mCRPC systemic treatment options by prior therapy and relevant biomarkers using data from 143 randomized trials. It serves as the first systematic resource designed to continuously adapt as new data emerges, ensuring relevance for clinical practice and providing clinicians with a synthesized and appraised, evidence-based framework to support data-driven management strategies for mCRPC (**Table 7**). Detailed results are hosted on an interactive website (**living website link**).

In patients **with prior ADT and *HRR* alterations**, the combination of PARPi and ARPIs have emerged as new options. However, it is important to emphasize that different *HRR* alterations are not equivalent in eliciting a response to PARPi[193]. Abiraterone+olaparib [65], enzalutamide+talazoparib [80], and niraparib+abiraterone [43] demonstrated rPFS benefit over ARPI alone, with a greater benefit in *BRCA 1/2* subgroup. Meta-analysis adjusting for subsequent life-prolonging therapies and cross-over in the MAGNITUDE trial [43] showed consistent benefit in *BRCA1/2* group **(Supplement Table 25)**. For non-*BRCA HRR* alterations, meta-analysis pooling evidence from the PROpel, TALAPRO-2 (cohort 2), and MAGNITUDE trials demonstrated an rPFS benefit in *CDK12* subgroup, and a potential signal of benefit in *PALB2* subgroup. However, no survival benefit was observed in *ATM* or *CHEK2* subgroups (**Supplement Tables 25**). These findings are consistent with the recent FDA pooled analysis [194]. Despite these analyses, the sample size for non-*BRCA HRR* genes was too small for a meaningful comparison. It is also important to consider the results

from the BRCAAway trial [183] which showed improved rPFS with concurrent use of olaparib and abiraterone compared to either of drugs used alone or in sequence. Taken together, these findings support the combined use of PARPi and ARPI in patients with *BRCA1/2*, *CDK12*, or *PALB2* gene alterations who have previously received ADT alone (**Table 7**).

In **patients with prior ADT and no *HRR* alterations**, ARPI like abiraterone acetate (COU-AA-302) [27,28] or enzalutamide (PREVAIL) [57] may be considered due to rPFS and OS benefit. Docetaxel [85] can also be considered in progressive disease after ADT while cabazitaxel should be relegated to post-docetaxel setting considering results from the FIRSTANA trial [34] which showed no survival advantage over docetaxel in chemo-naïve setting.

In patients **with prior ARPI and *HRR* alterations** particularly in *BRCA1/2* genes, adding a PARPi (olaparib/rucaparib) may be an effective option. The PROfound trial [60] reported an rPFS benefit with olaparib in overall population. However, only 3.4% of the cohort had received ARPIs in pre-mCRPC setting, highlighting a gap in data for upfront use. Likewise, the TRITON2 [195] and TRITON3 [86] trials showed a consistent effect with rucaparib in patients with *HRR* genes alterations, particularly in *BRCA1/2* genes. Although no OS benefit was seen in TRITON3 trial, likely due to extensive cross-over and receipt of subsequent life-prolonging therapies (**Supplement Table 26**), these data solidify rucaparib's role for *BRCA*-altered mCRPC, especially following ARPI failure. However, in *ATM*-altered cases, PARPi monotherapy did not show any survival benefit (**Supplement Table 27**). Given low representation of patients with prior ARPI in TALAPRO-2 [80], PROPEL [65], and MAGNITUDE [43] trials, the benefit with PARPi and

ARPI is not generalizable to patients with prior exposure to ARPI. Also, considering the established cross-resistance between sequential ARPIs, ARPI switching after failure is not preferred.

In patients with **prior ARPI and no *HRR* alterations,** docetaxel remains an established first-line mCRPC therapy as it was the preferred subsequent therapy in trials assessing ARPI+ADT in mHSPC (**Supplement Table 28**). Several studies have explored strategies continuing ARPI at progression while adding docetaxel or ^{177}Lu-PSMA-617 but none has showed definitive OS benefit. For example, PRESIDE [55] trial suggests modest rPFS benefit with the addition of docetaxel, while continuing enzalutamide beyond progression, although OS data were not reported. The phase II ABIDO-SOGUG [153] trial, did not meet the rPFS endpoint with the addition of docetaxel to abiraterone beyond progression. Moreover, emerging data from the phase III trial PSMAfore [97] demonstrated an rPFS benefit with ^{177}Lu-PSMA-617 following ARPI failure in PSMA+ mCRPC patients compared to switching to another ARPI; however, with no OS benefit likely due to high cross-over. Likewise, recent phase II ENZA-p trial [184] also showed that ^{177}Lu-PSMA-617 with enzalutamide improved PSA-PFS compared to enzalutamide alone in PSMA+ patients with high-risk features, though OS data are still pending. Despite advancements, limited data for ARPI-pretreated patients make optimizing post-ARPI treatment challenging, highlighting the need for randomized trials to define better options for these patients.

In patients **with prior docetaxel and *HRR* alterations** particularly in the *BRCA1/2* genes, PARPi with ARPI may be preferred. However, only 179 patients (22%) in PROpel, 179 (22%) in TALAPRO-2, and 85 (20%) in MAGNITUDE received prior

docetaxel in mHSPC (**Supplement Table 11**). Subgroup data for prior docetaxel from PROpel (olaparib + abiraterone), and TALAPRO-2 (talazoparib + enzalutamide) showed that the PARPi with ARPI improved rPFS compared to ARPI alone (**Tables 1 and 6**). However, the MAGNITUDE trial (niraparib + abiraterone) did not demonstrate an rPFS benefit in this patient population.

In patients **with prior docetaxel and no *HRR* alterations**, abiraterone acetate (COU-AA-301) [20] and enzalutamide (AFFIRM) [9] showed survival benefits and may be considered. An alternative option is cabazitaxel, as supported by the phase III TROPIC trial [87], which demonstrated improved survival compared to mitoxantrone in this patient population.

In patients **with both ARPI and docetaxel**, there is a lack of direct evidence for management of mCRPC. There are no trials specifically reporting outcomes in patients who have received 'true' triplet therapy as a single, combined approach in hormone-sensitive disease. Instead, the existing data mainly pertain to patients with mCRPC who have progressed sequentially on an ARPI and a taxane or vice versa, rather than in combination. **In patients with *HRR* alterations**, especially in the *BRCA1/2* genes, PARPi (olaparib/rucaparib) may be preferred given significant rPFS benefits in this population, as seen in the PROfound [60-64] and TRITON3 [86] trials. **In patients without *HRR* alterations,** ^{177}Lu-PSMA-617 offers survival benefits, as per results from the VISION trial [91]. Likewise, increased PSA response, without any survival benefit, was observed with ^{177}Lu-PSMA-617 compared to cabazitaxel in TheraP trial [158,159]. Hence, cabazitaxel remains a suitable option for patients who can tolerate it and is superior to a second ARPI after sub-optimal response to the first. The CARD trial [95] showed a

survival advantage with cabazitaxel over switching ARPI after progression with the caveat that the patients were required to have a sub-optimal response to the initial ARPI.

It is important to consider additional disease characteristics such as minimally symptomatic or bone only disease at progression. Radium-223 [13] improved OS and delayed skeletal related events in symptomatic bone metastases without nodal or visceral involvement (ALSYMPCA) and was safe in sequence with ^{177}Lu-PSMA-617 (RALU) [196]. The PEACE-3 trial [197] suggests combining radium-223 with enzalutamide reduces progression, though longer follow-up is needed for OS data, potentially offering a new first line option with a bone-protective agent and ADT, for ARPI-naïve mCRPC patients with bone metastases. Sipuleucel-T [29,36,93] may be limited to asymptomatic or minimally symptomatic disease, and pembrolizumab may be considered in high tumor mutational burden, dMMR or MSI-H patients who have been heavily pre-treated with standard therapies. However, these trials predate ARPI use or excluded prior ARPI, limiting relevance to current practice, where most patients will likely have progressed on an ARPI.

There are several strengths of our work. This 'living' review is the first comprehensive synthesis providing critically appraised randomized evidence from 141 clinical trials. Findings are organized and accessible through an interactive online platform, allowing users to filter data by variables like prior therapy, treatment type, specific treatments, control arms, and trial phase. As evidence in this field continues to evolve rapidly, with multiple phase III trials currently underway **(Supplement Table 29)**, this review is designed to incorporate new data using the living, interactive evidence

synthesis framework allowing timely updates, and ensuring that clinicians have access to the most current and comprehensive evidence available for managing mCRPC. While the discussion of using large language models for LSRs is beyond the scope of this review, emerging evidence suggests that human-artificial intelligence interaction can tremendously facilitate the process without compromising on accuracy [198].

There are a few limitations. Variations in the eligibility criteria of included trials limited quantitative synthesis of evidence by meta-analyses and consequently, outcomes for some therapies relied on data from single trials, leading to imprecision. There was inconsistent reporting of outcome and subgroup analyses across trials. Not all trials provided data on rPFS. While we assessed OS as a more definitive endpoint, survival may have been underestimated due to cross-over and subsequent life-prolonging therapies in certain trials (**Supplement Table 26**), which were not consistently adjusted across studies. Another limitation arises from the rapid evolution of prostate cancer treatment standards over the past decade. Even the latest mCRPC trials were conducted before the current treatment regimens for mHSPC were established. This creates challenges in applying these findings to contemporary settings, especially for patients who have undergone intensified upfront treatments. Hence, the lack of direct evidence for patients progressing on ARPI agents or triplet therapy in mHSPC lowers certainty of the evidence. Likewise, thresholds for categorizing patients into one of the five categories by receipt of prior therapy were finalized by consensus, which may be arbitrary and contributes to a degree of indirectness.

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Conflicts of Interest:

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Neeraj Agarwal (NA): NA received honorarium before May 2021 and during his lifetime for consulting to Astellas, AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics. He has also received research funding during his lifetime (to NA's institution) from Arnivas, Astellas, AstraZeneca, Bavarian Nordic, Bayer, Bristol Meyers Squibb, Calithera, Celldex, Clovis, CRISPR Therapeutics, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, Glaxo Smith Kline, Immunomedics, Janssen, Lava, Medivation, Merck, Nektar, Neoleukin, New Link Genetics, Novartis, Oric, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon.

Yousef Zakharia (YZ): YZ has received honoraria for data safety monitoring board membership from Janssen Research and Development. He has served as a consultant or advisor to Roche/Genentech, Eisai, Amgen, Castle Biosciences, Novartis, Exelixis, Pfizer, Cardinal Health, Bayer, Janssen, TTC Oncology, Clovis Oncology, EMD Serono, Seagen, Bristol Myers Squibb/Medarex, Myovant Sciences, Genzyme, Gilead Sciences, AstraZeneca and Array BioPharma. He has received research funding to his institution from Pfizer, Exelixis, and Eisai. His travel, accommodations, and expenses have been supported by Newlink Genetics.

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References

1. Freedland SJ, Davis M, Epstein AJ, Arondekar B, Ivanova JI. Real-world treatment patterns and overall survival among men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) in the US Medicare population. *Prostate Cancer Prostatic Dis.* 2024;27(2):327-333.
2. Riaz IB, Naqvi SAA, Hasan B, Murad MH. Future of Evidence Synthesis: Automated, Living, and Interactive Systematic Reviews and Meta-Analyses. *Mayo Clinic Proceedings: Digital Health.* 2024.
3. Riaz IB, He H, Ryu AJ, et al. A Living, Interactive Systematic Review and Network Meta-analysis of First-line Treatment of Metastatic Renal Cell Carcinoma. *Eur Urol.* 2021;80(6):712-723.
4. Riaz IB, Naqvi SAA, He H, et al. First-line Systemic Treatment Options for Metastatic Castration-Sensitive Prostate Cancer: A Living Systematic Review and Network Meta-analysis. *JAMA Oncol.* 2023;9(5):635-645.
5. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj.* 2021;372:n71.
6. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj.* 2019;366:l4898.
7. Saad F, Efstathiou E, Attard G, et al. Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo-controlled, double-blind, multinational, phase 3 study. *Lancet Oncol.* 2021;22(11):1541-1559.
8. Beer TM, Hotte SJ, Saad F, et al. Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): a randomised, open-label, international, phase 3 trial. *Lancet Oncol.* 2017;18(11):1532-1542.
9. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012;367(13):1187-1197.
10. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *Lancet Oncol.* 2014;15(10):1147-1156.
11. Morris MJ, Heller G, Hillman DW, et al. Randomized Phase III Study of Enzalutamide Compared With Enzalutamide Plus Abiraterone for Metastatic Castration-Resistant Prostate Cancer (Alliance A031201 Trial). *J Clin Oncol.* 2023;41(18):3352-3362.
12. Morris MJ, Heller G, Bryce AH, et al. Alliance A031201: A phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC). *Journal of Clinical Oncology.* 2019;37(15_suppl):5008-5008.
13. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.
14. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol.* 2014;15(12):1397-1406.
15. Scher HI, Jia X, Chi K, et al. Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. *J Clin Oncol.* 2011;29(16):2191-2198.

16. Beer TM, Kwon ED, Drake CG, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2017;35(1):40-47.
17. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol.* 2012;30(13):1534-1540.
18. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol.* 1999;17(8):2506-2513.
19. Smith M, De Bono J, Sternberg C, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. *J Clin Oncol.* 2016;34(25):3005-3013.
20. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364(21):1995-2005.
21. Logothetis C, Bono JSD, Molina A, et al. Effect of abiraterone acetate (AA) on pain control and skeletal-related events (SRE) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) post docetaxel (D): Results from the COU-AA-301 phase III study. *Journal of Clinical Oncology.* 2011;29(15_suppl):4520-4520.
22. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol.* 2012;13(12):1210-1217.
23. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2012;13(10):983-992.
24. Sternberg CN, Molina A, North S, et al. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Ann Oncol.* 2013;24(4):1017-1025.
25. Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. *Eur J Cancer.* 2013;49(17):3648-3657.
26. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013;368(2):138-148.
27. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol.* 2014;66(5):815-825.
28. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2015;16(2):152-160.
29. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol.* 2006;24(19):3089-3094.
30. Saad F, Fizazi K, Jinga V, et al. Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. *Lancet Oncol.* 2015;16(3):338-348.

31. Fizazi K, Jones R, Oudard S, et al. Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. *J Clin Oncol.* 2015;33(7):723-731.
32. Fizazi K, Higano CS, Nelson JB, et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2013;31(14):1740-1747.
33. Nelson JB, Fizazi K, Miller K, et al. Phase 3, randomized, placebo-controlled study of zibotentan (ZD4054) in patients with castration-resistant prostate cancer metastatic to bone. *Cancer.* 2012;118(22):5709-5718.
34. Oudard S, Fizazi K, Sengeløv L, et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. *J Clin Oncol.* 2017;35(28):3189-3197.
35. Powles T, Yuen KC, Gillessen S, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. *Nat Med.* 2022;28(1):144-153.
36. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363(5):411-422.
37. Sweeney C, Bracarda S, Sternberg CN, et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. *Lancet.* 2021;398(10295):131-142.
38. Antonarakis ES, Park SH, Goh JC, et al. Pembrolizumab Plus Olaparib for Patients With Previously Treated and Biomarker-Unselected Metastatic Castration-Resistant Prostate Cancer: The Randomized, Open-Label, Phase III KEYLYNK-010 Trial. *J Clin Oncol.* 2023;41(22):3839-3850.
39. Mehra N, Antonarakis ES, Park SH, et al. Patient-reported outcomes (PROs) in KEYLYNK-010: Pembrolizumab (pembro) plus olaparib (ola) vs abiraterone acetate (abi) or enzalutamide (enza) for patients (pts) with previously treated metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology.* 2023;41(6_suppl):131-131.
40. Chi KN, Rathkopf DE, Smith MR, et al. Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. *Journal of Clinical Oncology.* 2022;40(6_suppl):12-12.
41. Efstathiou E, Smith MR, Sandhu S, et al. Niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations: Second interim analysis (IA2) of MAGNITUDE. *Journal of Clinical Oncology.* 2023;41(6_suppl):170-170.
42. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2023;41(18):3339-3351.
43. Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. *Ann Oncol.* 2023;34(9):772-782.
44. Sandhu S, Attard G, Olmos D, et al. Gene-by-gene analysis in the MAGNITUDE study of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations. *Journal of Clinical Oncology.* 2022;40(16_suppl):5020-5020.

45. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2015;16(4):417-425.
46. Carducci MA, Saad F, Abrahamsson PA, et al. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer.* 2007;110(9):1959-1966.
47. Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, et al. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. *Lancet Oncol.* 2013;14(2):117-124.
48. Leaf AN, Propert K, Corcoran C, et al. Phase III study of combined chemohormonal therapy in metastatic prostate cancer (ECOG 3882): an Eastern Cooperative Oncology Group study. *Med Oncol.* 2003;20(2):137-146.
49. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. *J Urol.* 2002;168(6):2439-2443.
50. Michaelson MD, Oudard S, Ou YC, et al. Randomized, placebo-controlled, phase III trial of sunitinib plus prednisone versus prednisone alone in progressive, metastatic, castration-resistant prostate cancer. *J Clin Oncol.* 2014;32(2):76-82.
51. Small EJ, Meyer M, Marshall ME, et al. Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol.* 2000;18(7):1440-1450.
52. Sternberg C, Armstrong A, Pili R, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Study of Tasquinimod in Men With Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2016;34(22):2636-2643.
53. Abratt RP, Brune D, Dimopoulos MA, et al. Randomised phase III study of intravenous vinorelbine plus hormone therapy versus hormone therapy alone in hormone-refractory prostate cancer. *Ann Oncol.* 2004;15(11):1613-1621.
54. Mathew P, Thall PF, Bucana CD, et al. Platelet-derived growth factor receptor inhibition and chemotherapy for castration-resistant prostate cancer with bone metastases. *Clin Cancer Res.* 2007;13(19):5816-5824.
55. Merseburger AS, Attard G, Åström L, et al. Continuous enzalutamide after progression of metastatic castration-resistant prostate cancer treated with docetaxel (PRESIDE): an international, randomised, phase 3b study. *Lancet Oncol.* 2022;23(11):1398-1408.
56. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014;371(5):424-433.
57. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol.* 2017;71(2):151-154.
58. Cash H, Steiner U, Heidenreich A, et al. Intermittent vs continuous docetaxel therapy in patients with metastatic castration-resistant prostate cancer - a phase III study (PRINCE). *BJU Int.* 2018;122(5):774-782.
59. Bono JSD, Fizazi K, Saad F, et al. PROfound: Efficacy of olaparib (ola) by prior taxane use in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations. *Journal of Clinical Oncology.* 2020;38(6_suppl):134-134.
60. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2020;382(22):2091-2102.
61. Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2020;383(24):2345-2357.

62. Bono JSD, Matsubara N, Penel N, et al. Exploratory gene-by-gene analysis of olaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): PROfound. *Journal of Clinical Oncology.* 2021;39(6_suppl):126-126.
63. Matsubara N, Bono JSD, Olmos D, et al. Olaparib efficacy in patients with metastatic castration-resistant prostate cancer (mCRPC) carrying circulating tumor (ct) DNA alterations in *BRCA1*, *BRCA2* or *ATM*: Results from the PROfound study. *Journal of Clinical Oncology.* 2021;39(6_suppl):27-27.
64. Mateo J, de Bono JS, Fizazi K, et al. Olaparib for the Treatment of Patients With Metastatic Castration-Resistant Prostate Cancer and Alterations in BRCA1 and/or BRCA2 in the PROfound Trial. *J Clin Oncol.* 2024;42(5):571-583.
65. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. *NEJM Evid.* 2022;1(9):EVIDoa2200043.
66. Saad F, Armstrong AJ, Thiery-Vuillemin A, et al. PROpel: Phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology.* 2022;40(6_suppl):11-11.
67. Oya M, Armstrong AJ, Thiery-Vuillemin A, et al. 157O Biomarker analysis and updated results from the phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Annals of Oncology.* 2022;33:S1495.
68. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Final overall survival (OS) in PROpel: Abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology.* 2023;41(6_suppl):LBA16-LBA16.
69. Saad F, Clarke NW, Oya M, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2023;24(10):1094-1108.
70. Shore ND, Clarke N, Armstrong AJ, et al. Efficacy of olaparib (O) plus abiraterone (A) versus placebo (P) plus A in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with single homologous recombination repair gene mutations (HRRm) in the PROpel trial. *Journal of Clinical Oncology.* 2024;42(4_suppl):165-165.
71. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m(2)) and the Currently Approved Dose (25 mg/m(2)) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer-PROSELICA. *J Clin Oncol.* 2017;35(28):3198-3206.
72. Gulley JL, Borre M, Vogelzang NJ, et al. Phase III Trial of PROSTVAC in Asymptomatic or Minimally Symptomatic Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2019;37(13):1051-1061.
73. Araujo JC, Trudel GC, Saad F, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *Lancet Oncol.* 2013;14(13):1307-1316.
74. Cathomas R, Crabb SJ, Mark M, et al. Orteronel Switch Maintenance Therapy in Metastatic Castration Resistant Prostate Cancer After First-Line Docetaxel: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial (SAKK 08/11). *Prostate.* 2016;76(16):1519-1527.
75. Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol.* 2009;27(32):5431-5438.

76. Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(9):893-900.
77. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351(15):1513-1520.
78. Chi KN, Higano CS, Blumenstein B, et al. Custirsen in combination with docetaxel and prednisone for patients with metastatic castration-resistant prostate cancer (SYNERGY trial): a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol.* 2017;18(4):473-485.
79. Fizazi K, Azad A, Matsubara N, et al. TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) harboring homologous recombination repair (HRR) gene alterations. *Journal of Clinical Oncology.* 2023;41(16_suppl):5004-5004.
80. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet.* 2023;402(10398):291-303.
81. Fizazi K, Azad AA, Matsubara N, et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. *Nat Med.* 2024;30(1):257-264.
82. Shore ND, Agarwal N, Azad A, et al. Post hoc analysis of rPFS and OS from the TALAPRO-2 (TP-2) study: Genomic subgroups based on likelihood of *BRCA* or HRR gene alteration status. *Journal of Clinical Oncology.* 2024;42(4_suppl):136-136.
83. Zschaebitz S, Fizazi K, Matsubara N, et al. Exploratory analyses of homologous recombination repair (HRR) gene subgroups and potential associations with secondary efficacy endpoints in the HRR-deficient population from TALAPRO-2. *Journal of Clinical Oncology.* 2024;42(4_suppl):178-178.
84. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351(15):1502-1512.
85. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol.* 2008;26(2):242-245.
86. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or Physician's Choice in Metastatic Prostate Cancer. *N Engl J Med.* 2023;388(8):719-732.
87. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010;376(9747):1147-1154.
88. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol.* 2013;24(9):2402-2408.
89. Tannock IF, Fizazi K, Ivanov S, et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *Lancet Oncol.* 2013;14(8):760-768.
90. Vogelzang NJ, Beer TM, Gerritsen W, et al. Efficacy and Safety of Autologous Dendritic Cell-Based Immunotherapy, Docetaxel, and Prednisone vs Placebo in Patients With Metastatic Castration-Resistant Prostate Cancer: The VIABLE Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2022;8(4):546-552.
91. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2021;385(12):1091-1103.

92. Fizazi K, Herrmann K, Krause BJ, et al. Health-related quality of life and pain outcomes with [(177)Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2023;24(6):597-610.
93. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer.* 2009;115(16):3670-3679.
94. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(3):408-419.
95. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. *N Engl J Med.* 2019;381(26):2506-2518.
96. Fizazi K, Kramer G, Eymard JC, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. *Lancet Oncol.* 2020;21(11):1513-1525.
97. Morris MJ, Castellano D, Herrmann K, et al. (177)Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. *Lancet.* 2024;404(10459):1227-1239.
98. Fizazi K, Morris MJ, Shore ND, et al. Health-related quality of life and pain in a phase 3 study of [^{177}Lu]Lu-PSMA-617 in taxane-naïve patients with metastatic castration-resistant prostate cancer (PSMAfore). *Journal of Clinical Oncology.* 2024;42(16_suppl):5003-5003.
99. Denmeade SR, Wang H, Agarwal N, et al. TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men With Castration-Resistant Metastatic Prostate Cancer. *J Clin Oncol.* 2021;39(12):1371-1382.
100. Pili R, Rosenthal MA, Mainwaring PN, et al. Phase II study on the addition of ASA404 (vadimezan; 5,6-dimethylxanthenone-4-acetic acid) to docetaxel in CRMPC. *Clin Cancer Res.* 2010;16(10):2906-2914.
101. Small EJ, Lance RS, Gardner TA, et al. A Randomized Phase II Trial of Sipuleucel-T with Concurrent versus Sequential Abiraterone Acetate plus Prednisone in Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res.* 2015;21(17):3862-3869.
102. Antonarakis ES, Subudhi SK, Pieczonka CM, et al. Combination Treatment with Sipuleucel-T and Abiraterone Acetate or Enzalutamide for Metastatic Castration-Resistant Prostate Cancer: STAMP and STRIDE Trials. *Clin Cancer Res.* 2023;29(13):2426-2434.
103. Heidenreich A, Sommer F, Ohlmann CH, et al. Prospective randomized Phase II trial of pegylated doxorubicin in the management of symptomatic hormone-refractory prostate carcinoma. *Cancer.* 2004;101(5):948-956.
104. Spetsieris N, Boukovala M, Weldon JA, et al. A Phase 2 Trial of Abiraterone Followed by Randomization to Addition of Dasatinib or Sunitinib in Men With Metastatic Castration-Resistant Prostate Cancer. *Clin Genitourin Cancer.* 2021;19(1):22-31.e25.
105. Crabb SJ, Griffiths G, Marwood E, et al. Pan-AKT Inhibitor Capivasertib With Docetaxel and Prednisolone in Metastatic Castration-Resistant Prostate Cancer: A Randomized, Placebo-Controlled Phase II Trial (ProCAID). *J Clin Oncol.* 2021;39(3):190-201.
106. Crabb SJ, Griffiths G, Dunkley D, et al. Overall Survival Update for Patients with Metastatic Castration-resistant Prostate Cancer Treated with Capivasertib and Docetaxel in the Phase 2 ProCAID Clinical Trial. *Eur Urol.* 2022;82(5):512-515.

107. Annala M, Fu S, Bacon JVW, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase II trial. *Ann Oncol.* 2021;32(7):896-905.
108. Dahut WL, Gulley JL, Arlen PM, et al. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol.* 2004;22(13):2532-2539.
109. Machiels JP, Mazzeo F, Clausse M, et al. Prospective randomized study comparing docetaxel, estramustine, and prednisone with docetaxel and prednisone in metastatic hormone-refractory prostate cancer. *J Clin Oncol.* 2008;26(32):5261-5268.
110. Eigl BJ, Chi K, Tu D, et al. A randomized phase II study of pelareorep and docetaxel or docetaxel alone in men with metastatic castration resistant prostate cancer: CCTG study IND 209. *Oncotarget.* 2018;9(8):8155-8164.
111. Berry WR, Hathorn JW, Dakhil SR, et al. Phase II randomized trial of weekly paclitaxel with or without estramustine phosphate in progressive, metastatic, hormone-refractory prostate cancer. *Clin Prostate Cancer.* 2004;3(2):104-111.
112. Droz JP, Medioni J, Chevreau C, et al. Randomized phase II study of nintedanib in metastatic castration-resistant prostate cancer postdocetaxel. *Anticancer Drugs.* 2014;25(9):1081-1088.
113. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2010;28(7):1099-1105.
114. Fizazi K, De Bono JS, Flechon A, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. *Eur J Cancer.* 2012;48(1):85-93.
115. James ND, Caty A, Borre M, et al. Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: a double-blind, placebo-controlled, randomised, phase 2 trial. *Eur Urol.* 2009;55(5):1112-1123.
116. James ND, Caty A, Payne H, et al. Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: a double-blind, placebo-controlled, randomized Phase II trial. *BJU Int.* 2010;106(7):966-973.
117. Albrecht W, Van Poppel H, Horenblas S, et al. Randomized Phase II trial assessing estramustine and vinblastine combination chemotherapy vs estramustine alone in patients with progressive hormone-escaped metastatic prostate cancer. *Br J Cancer.* 2004;90(1):100-105.
118. Cabrespine A, Guy L, Khenifar E, et al. Randomized Phase II study comparing paclitaxel and carboplatin versus mitoxantrone in patients with hormone-refractory prostate cancer. *Urology.* 2006;67(2):354-359.
119. Venkitaraman R, Lorente D, Murthy V, et al. A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. *Eur Urol.* 2015;67(4):673-679.
120. Azad AA, Beardsley EK, Hotte SJ, et al. A randomized phase II efficacy and safety study of vandetanib (ZD6474) in combination with bicalutamide versus bicalutamide alone in patients with chemotherapy naïve castration-resistant prostate cancer. *Invest New Drugs.* 2014;32(4):746-752.
121. DiPaola RS, Chen YH, Stein M, et al. A randomized phase II trial of mitoxantrone, estramustine and vinorelbine or bcl-2 modulation with 13-cis retinoic acid, interferon and

paclitaxel in patients with metastatic castrate-resistant prostate cancer: ECOG 3899. *J Transl Med.* 2010;8:20.

122. Boccardo F, Rubagotti A, Conti G, et al. Prednisone plus gefitinib versus prednisone plus placebo in the treatment of hormone-refractory prostate cancer: a randomized phase II trial. *Oncology.* 2008;74(3-4):223-228.
123. Chi KN, Hotte SJ, Yu EY, et al. Randomized phase II study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2010;28(27):4247-4254.
124. Hakenberg OW, Perez-Gracia JL, Castellano D, et al. Randomised phase II study of second-line olaratumab with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. *Eur J Cancer.* 2019;107:186-195.
125. Attia S, Eickhoff J, Wilding G, et al. Randomized, double-blinded phase II evaluation of docetaxel with or without doxercalciferol in patients with metastatic, androgen-independent prostate cancer. *Clin Cancer Res.* 2008;14(8):2437-2443.
126. Patel SR, Kvols LK, Hahn RG, Windschitl H, Levitt R, Therneau T. A phase II randomized trial of megestrol acetate or dexamethasone in the treatment of hormonally refractory advanced carcinoma of the prostate. *Cancer.* 1990;66(4):655-658.
127. Takahashi M, Kawabata R, Kawano A, et al. Substitution of anti-androgens and tegafur-uracil combination therapy for castration-resistant prostate cancer: results of a multi-center randomized phase II study. *Int J Oncol.* 2013;43(3):713-720.
128. Millikan R, Thall PF, Lee SJ, et al. Randomized, multicenter, phase II trial of two multicomponent regimens in androgen-independent prostate cancer. *J Clin Oncol.* 2003;21(5):878-883.
129. van Dodewaard-de Jong JM, de Klerk JMH, Bloemendal HJ, et al. A randomised, phase II study of repeated rhenium-188-HEDP combined with docetaxel and prednisone versus docetaxel and prednisone alone in castration-resistant prostate cancer (CRPC) metastatic to bone; the Taxium II trial. *Eur J Nucl Med Mol Imaging.* 2017;44(8):1319-1327.
130. Saad F, Hotte S, North S, et al. Randomized phase II trial of Custirsen (OGX-011) in combination with docetaxel or mitoxantrone as second-line therapy in patients with metastatic castrate-resistant prostate cancer progressing after first-line docetaxel: CUOG trial P-06c. *Clin Cancer Res.* 2011;17(17):5765-5773.
131. Dorff TB, Quinn DI, Pinski JK, et al. Randomized Phase II Trial of Abiraterone Alone or With Dasatinib in Men With Metastatic Castration-resistant Prostate Cancer (mCRPC). *Clin Genitourin Cancer.* 2019;17(4):241-247.e241.
132. Passildas-Jahanmohan J, Eymard JC, Pouget M, et al. Multicenter randomized phase II study comparing docetaxel plus curcumin versus docetaxel plus placebo in first-line treatment of metastatic castration-resistant prostate cancer. *Cancer Med.* 2021;10(7):2332-2340.
133. Monk P, Liu G, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tivantinib in men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). *Invest New Drugs.* 2018;36(5):919-926.
134. Stadler WM, Cao D, Vogelzang NJ, et al. A randomized Phase II trial of the antiangiogenic agent SU5416 in hormone-refractory prostate cancer. *Clin Cancer Res.* 2004;10(10):3365-3370.
135. Hussain M, Le Moulec S, Gimmi C, Bruns R, Straub J, Miller K. Differential Effect on Bone Lesions of Targeting Integrins: Randomized Phase II Trial of Abituzumab in Patients with Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res.* 2016;22(13):3192-3200.

136. McNeel DG, Chen YH, Gulley JL, et al. Randomized phase II trial of docetaxel with or without PSA-TRICOM vaccine in patients with castrate-resistant metastatic prostate cancer: A trial of the ECOG-ACRIN cancer research group (E1809). *Hum Vaccin Immunother.* 2015;11(10):2469-2474.
137. Antonarakis ES, Heath EI, Smith DC, et al. Repurposing itraconazole as a treatment for advanced prostate cancer: a noncomparative randomized phase II trial in men with metastatic castration-resistant prostate cancer. *Oncologist.* 2013;18(2):163-173.
138. Nelius T, Klatte T, Yap R, et al. A randomized study of docetaxel and dexamethasone with low- or high-dose estramustine for patients with advanced hormone-refractory prostate cancer. *BJU Int.* 2006;98(3):580-585.
139. Oudard S, Banu E, Beuzeboc P, et al. Multicenter randomized phase II study of two schedules of docetaxel, estramustine, and prednisone versus mitoxantrone plus prednisone in patients with metastatic hormone-refractory prostate cancer. *J Clin Oncol.* 2005;23(15):3343-3351.
140. Filaci G, Fenoglio D, Nolè F, et al. Telomerase-based GX301 cancer vaccine in patients with metastatic castration-resistant prostate cancer: a randomized phase II trial. *Cancer Immunol Immunother.* 2021;70(12):3679-3692.
141. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol.* 2019;20(12):1730-1739.
142. Kongsted P, Borch TH, Ellebaek E, et al. Dendritic cell vaccination in combination with docetaxel for patients with metastatic castration-resistant prostate cancer: A randomized phase II study. *Cytotherapy.* 2017;19(4):500-513.
143. Smith DC, Smith MR, Sweeney C, et al. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. *J Clin Oncol.* 2013;31(4):412-419.
144. Antonarakis ES, Tagawa ST, Galletti G, et al. Randomized, Noncomparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2017;35(28):3181-3188.
145. Corn PG, Heath EI, Zurita A, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1-2 trial. *Lancet Oncol.* 2019;20(10):1432-1443.
146. Sternberg CN, Dumez H, Van Poppel H, et al. Docetaxel plus oblimersen sodium (Bcl-2 antisense oligonucleotide): an EORTC multicenter, randomized phase II study in patients with castration-resistant prostate cancer. *Ann Oncol.* 2009;20(7):1264-1269.
147. Pili R, Häggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *J Clin Oncol.* 2011;29(30):4022-4028.
148. Armstrong AJ, Häggman M, Stadler WM, et al. Long-term survival and biomarker correlates of tasquinimod efficacy in a multicenter randomized study of men with minimally symptomatic metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2013;19(24):6891-6901.
149. Beer TM, Ryan CW, Venner PM, et al. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. *J Clin Oncol.* 2007;25(6):669-674.
150. Fosså SD, Jacobsen AB, Ginman C, et al. Weekly docetaxel and prednisolone versus prednisolone alone in androgen-independent prostate cancer: a randomized phase II study. *Eur Urol.* 2007;52(6):1691-1698.

151. Sonpavde G, Matveev V, Burke JM, et al. Randomized phase II trial of docetaxel plus prednisone in combination with placebo or AT-101, an oral small molecule Bcl-2 family antagonist, as first-line therapy for metastatic castration-resistant prostate cancer. *Ann Oncol.* 2012;23(7):1803-1808.
152. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol.* 2016;17(2):153-163.
153. Climent MA, Font A, Durán I, et al. A phase II randomised trial of abiraterone acetate plus prednisone in combination with docetaxel or docetaxel plus prednisone after disease progression to abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer: The ABIDO-SOGUG trial. *Eur J Cancer.* 2022;175:110-119.
154. Gillessen S, Procopio G, Hayoz S, et al. Darolutamide Maintenance in Patients With Metastatic Castration-Resistant Prostate Cancer With Nonprogressive Disease After Taxane Treatment (SAKK 08/16). *J Clin Oncol.* 2023;41(20):3608-3615.
155. Lara PN, Jr., Stadler WM, Longmate J, et al. A randomized phase II trial of the matrix metalloproteinase inhibitor BMS-275291 in hormone-refractory prostate cancer patients with bone metastases. *Clin Cancer Res.* 2006;12(5):1556-1563.
156. Dimopoulos MA, Kiamouris C, Gika D, et al. Combination of LHRH analog with somatostatin analog and dexamethasone versus chemotherapy in hormone-refractory prostate cancer: a randomized phase II study. *Urology.* 2004;63(1):120-125.
157. Millikan R, Baez L, Banerjee T, et al. Randomized phase 2 trial of ketoconazole and ketoconazole/doxorubicin in androgen independent prostate cancer. *Urol Oncol.* 2001;6(3):111-115.
158. Hofman MS, Emmett L, Sandhu S, et al. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet.* 2021;397(10276):797-804.
159. Hofman MS, Emmett L, Sandhu S, et al. Overall survival with [(177)Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. *Lancet Oncol.* 2024;25(1):99-107.
160. de Bono JS, Piulats JM, Pandha HS, et al. Phase II randomized study of figitumumab plus docetaxel and docetaxel alone with crossover for metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2014;20(7):1925-1934.
161. Figg WD, Dahut W, Duray P, et al. A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. *Clin Cancer Res.* 2001;7(7):1888-1893.
162. Arlen PM, Gulley JL, Parker C, et al. A randomized phase II study of concurrent docetaxel plus vaccine versus vaccine alone in metastatic androgen-independent prostate cancer. *Clin Cancer Res.* 2006;12(4):1260-1269.
163. Bouman-Wammes EW, van den Berg HP, de Munck L, et al. A randomised phase II trial of docetaxel versus docetaxel plus carboplatin in patients with castration-resistant prostate cancer who have progressed after response to prior docetaxel chemotherapy: The RECARDO trial. *Eur J Cancer.* 2018;90:1-9.
164. Sridhar SS, Joshua AM, Gregg R, et al. A phase II study of GW786034 (pazopanib) with or without bicalutamide in patients with castration-resistant prostate cancer. *Clin Genitourin Cancer.* 2015;13(2):124-129.
165. Yoshimura K, Minami T, Nozawa M, et al. A Phase 2 Randomized Controlled Trial of Personalized Peptide Vaccine Immunotherapy with Low-dose Dexamethasone Versus Dexamethasone Alone in Chemotherapy-naive Castration-resistant Prostate Cancer. *Eur Urol.* 2016;70(1):35-41.

166. Meulenbeld HJ, Bleuse JP, Vinci EM, et al. Randomized phase II study of danusertib in patients with metastatic castration-resistant prostate cancer after docetaxel failure. *BJU Int.* 2013;111(1):44-52.
167. Joly F, Delva R, Mourey L, et al. Clinical benefits of non-taxane chemotherapies in unselected patients with symptomatic metastatic castration-resistant prostate cancer after docetaxel: the GETUG-P02 study. *BJU Int.* 2015;115(1):65-73.
168. Droz JP, Muracciole X, Mottet N, et al. Phase II study of oxaliplatin versus oxaliplatin combined with infusional 5-fluorouracil in hormone refractory metastatic prostate cancer patients. *Ann Oncol.* 2003;14(8):1291-1298.
169. Carducci MA, Padley RJ, Breul J, et al. Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol.* 2003;21(4):679-689.
170. Krainer M, Tomek S, Elandt K, et al. A prospective, open label, randomized phase II trial of weekly docetaxel versus weekly vinorelbine as first line chemotherapy in patients with androgen independent prostate cancer. *J Urol.* 2007;177(6):2141-2145; discussion 2145.
171. Yu EY, Ellard SL, Hotte SJ, et al. A randomized phase 2 study of a HSP27 targeting antisense, apatorsen with prednisone versus prednisone alone, in patients with metastatic castration resistant prostate cancer. *Invest New Drugs.* 2018;36(2):278-287.
172. Yachnin J, Gilje B, Thon K, et al. Weekly versus 3-weekly cabazitaxel for the treatment of castration-resistant prostate cancer: A randomised phase II trial (ConCab). *Eur J Cancer.* 2018;97:33-40.
173. Galsky MD, Small EJ, Oh WK, et al. Multi-institutional randomized phase II trial of the epothilone B analog ixabepilone (BMS-247550) with or without estramustine phosphate in patients with progressive castrate metastatic prostate cancer. *J Clin Oncol.* 2005;23(7):1439-1446.
174. Heidenreich A, Rawal SK, Szkarlat K, et al. A randomized, double-blind, multicenter, phase 2 study of a human monoclonal antibody to human αv integrins (intetumumab) in combination with docetaxel and prednisone for the first-line treatment of patients with metastatic castration-resistant prostate cancer. *Ann Oncol.* 2013;24(2):329-336.
175. Figg WD, Liu Y, Arlen P, et al. A randomized, phase II trial of ketoconazole plus alendronate versus ketoconazole alone in patients with androgen independent prostate cancer and bone metastases. *J Urol.* 2005;173(3):790-796.
176. Bradley DA, Daignault S, Ryan CJ, et al. Cilengitide (EMD 121974, NSC 707544) in asymptomatic metastatic castration resistant prostate cancer patients: a randomized phase II trial by the prostate cancer clinical trials consortium. *Invest New Drugs.* 2011;29(6):1432-1440.
177. Tolcher AW, Reyno L, Venner PM, et al. A randomized phase II and pharmacokinetic study of the antisense oligonucleotides ISIS 3521 and ISIS 5132 in patients with hormone-refractory prostate cancer. *Clin Cancer Res.* 2002;8(8):2530-2535.
178. Eymard JC, Priou F, Zannetti A, et al. Randomized phase II study of docetaxel plus estramustine and single-agent docetaxel in patients with metastatic hormone-refractory prostate cancer. *Ann Oncol.* 2007;18(6):1064-1070.
179. Horti J, Widmark A, Stenzl A, et al. A randomized, double-blind, placebo-controlled phase II study of vandetanib plus docetaxel/prednisolone in patients with hormone-refractory prostate cancer. *Cancer Biother Radiopharm.* 2009;24(2):175-180.
180. Omlin A, Cathomas R, von Amsberg G, et al. Randomized Phase II Cabazitaxel Dose Individualization and Neutropenia Prevention Trial in Patients with Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res.* 2023;29(10):1887-1893.
181. Wiechno P, Somer BG, Mellado B, et al. A randomised phase 2 study combining LY2181308 sodium (survivin antisense oligonucleotide) with first-line

docetaxel/prednisone in patients with castration-resistant prostate cancer. *Eur Urol.* 2014;65(3):516-520.
182. Rosenberg JE, Weinberg VK, Kelly WK, et al. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients : randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. *Cancer.* 2007;110(3):556-563.
183. Hussain M, Kocherginsky M, Agarwal N, et al. Abiraterone, Olaparib, or Abiraterone + Olaparib in First-Line Metastatic Castration-Resistant Prostate Cancer with DNA Repair Defects (BRCAAway). *Clin Cancer Res.* 2024;30(19):4318-4328.
184. Emmett L, Subramaniam S, Crumbaker M, et al. [(177)Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2024;25(5):563-571.
185. Caffo O, Ortega C, Nolè F, et al. Docetaxel and prednisone with or without enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer: CHEIRON, a randomised phase II trial. *Eur J Cancer.* 2021;155:56-63.
186. Attard G, Borre M, Gurney H, et al. Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment. *J Clin Oncol.* 2018;36(25):2639-2646.
187. Hussain MHA, Kocherginsky M, Agarwal N, et al. BRCAAway: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) bearing homologous recombination-repair mutations (HRRm). *Journal of Clinical Oncology.* 2024;42(4_suppl):19-19.
188. Fizazi K, Azad A, Matsubara N, et al. Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line (1L) treatment in patients (pts) with homologous recombination repair (HRR)-deficient metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial. *Journal of Clinical Oncology.* 2025;43(5_suppl):LBA141-LBA141.
189. Agarwal N, Azad A, Carles J, et al. Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial. *Journal of Clinical Oncology.* 2025;43(5_suppl):LBA18-LBA18.
190. Emmett L, Subramaniam S, Crumbaker M, et al. Overall survival and quality of life with [(177)Lu]Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2025;26(3):291-299.
191. Petrylak DP, Ratta R, Matsubara N, et al. Pembrolizumab Plus Docetaxel Versus Docetaxel for Previously Treated Metastatic Castration-Resistant Prostate Cancer: The Randomized, Double-Blind, Phase III KEYNOTE-921 Trial. *J Clin Oncol.* 2025:Jco2401283.
192. Rescigno P, Porta N, Finneran L, et al. Capivasertib in combination with enzalutamide for metastatic castration resistant prostate cancer after docetaxel and abiraterone: Results from the randomized phase II RE-AKT trial. *Eur J Cancer.* 2024;205:114103.
193. Naqvi SAA, Riaz IB, Bibi A, et al. Heterogeneity of the Treatment Effect with PARP Inhibitors in Metastatic Castration-resistant Prostate Cancer: A Living Interactive Systematic Review and Meta-analysis. *Eur Urol.* 2025.
194. Fallah J, Xu J, Weinstock C, et al. Efficacy of Poly(ADP-ribose) Polymerase Inhibitors by Individual Genes in Homologous Recombination Repair Gene-Mutated Metastatic Castration-Resistant Prostate Cancer: A US Food and Drug Administration Pooled Analysis. *J Clin Oncol.* 2024;42(14):1687-1698.
195. Abida W, Campbell D, Patnaik A, et al. Rucaparib for the Treatment of Metastatic Castration-resistant Prostate Cancer Associated with a DNA Damage Repair Gene

Alteration: Final Results from the Phase 2 TRITON2 Study. *Eur Urol.* 2023;84(3):321-330.

196. Rahbar K, Essler M, Pabst KM, et al. Safety and Survival Outcomes of (177)Lu-Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer with Prior (223)Ra treatment: The RALU Study. *J Nucl Med.* 2023;64(4):574-578.
197. Gillessen S, Choudhury A, Saad F, et al. LBA1 A randomized multicenter open label phase III trial comparing enzalutamide vs a combination of Radium-223 (Ra223) and enzalutamide in asymptomatic or mildly symptomatic patients with bone metastatic castration-resistant prostate cancer (mCRPC): First results of EORTC-GUCG 1333/PEACE-3. *Annals of Oncology.* 2024;35:S1254.
198. Khan MA, Ayub U, Naqvi SAA, et al. Collaborative Large Language Models for Automated Data Extraction in Living Systematic Reviews. *medRxiv.* 2024.
199. Francolini G, Allegra AG, Detti B, et al. Stereotactic Body Radiation Therapy and Abiraterone Acetate for Patients Affected by Oligometastatic Castrate-Resistant Prostate Cancer: A Randomized Phase II Trial (ARTO). *J Clin Oncol.* 2023;41(36):5561-5568.
200. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol.* 2020;38(1):1-10.

Tables

Figures

Figure 1. PRISMA flowchart outlining the study selection process

Table 1. Summary of characteristics and results of included phase III trials in which patients received prior ADT only

Trial	Arm	Estimated /Actual Accrual	Years of enrollment	Median follow up - months	Primary Endpoint	OS HR (95% CI)	PFS HR (95% CI)	Prior therapy | %
ARPI monotherapy								
COU-AA-302, 2013	Rx: Abiraterone Ctrl: Placebo	1000/ 1088	04/01/2009- 06/01/2010	49.2	OS; rPFS *	34.7 vs. 30.3 0.81 (0.70-0.93) †	16.5 vs. 8.2 § 0.52 (0.45-0.61)	ADT: 100
PREVAIL, 2014	Rx: Enzalutamide Ctrl: Placebo	1680/ 1717	09/01/2010- 09/01/2012	Rx: 22; Ctrl: 26.5	OS; rPFS	35.3 vs. 31.3 0.77 (0.67-0.88) †	20 vs 5.4 § 0.32 (0.28-0.36)	ADT: 100
ELM-PC 4, 2015	Rx: TAK-700 Ctrl: Placebo	1454/ 1560	10/31/2010- 06/29/2012	8.4	OS; rPFS	31.4 vs. 29.5 0.92 (0.79-1.08)	13.8 vs. 8.7 § 0.71 (0.63-0.80)	ADT: 100
ARPI+ARPI								
ACIS, 2021	Rx: Abiraterone + Apalutamide Ctrl: Abiraterone	400/ 982	12/10/2014- 08/30/2016	54.8	rPFS	36.2 vs. 33.7 0.95 (0.81-1.11)	22 vs. 19.2 § 0.86 (0.72-1.04)	ADT: 100
AllianceA031201, 2023	Rx: Enzalutamide + Abiraterone Ctrl: Enzalutamide	1224/ 1311	01/28/2014- 08/31/2016	60.6	OS	34.2 vs. 32.7 0.89 (0.78-1.01)	24.3 vs. 21.3 § 0.86 (0.76-0.97)	ADT: 100
ARPI+PI3K/AKTi								
IPATential150, 2021	Rx: Abiraterone + Ipatasertib Ctrl: Abiraterone	1100/ 1101	06/30/2017- 01/17/2019	19	rPFS ‡	NR vs. NR 0.93 (0.73-1.18)	19.2 vs. 16.6 § 0.82 (0.68-0.99)	ADT: 100 Docetaxel: 18
ARPI+Radiopharmaceutical								
ERA 223, 2019	Rx: Abiraterone + Radium-223 Ctrl: Abiraterone	800/ 806	03/30/2014- 08/12/2016	Rx: 20.6; Ctrl: 21.7	SSE-free survival	30.7 vs. 33.3 1.19 (0.95-1.50)	11.2 vs.12.4 § 1.15 (0.96-1.38)	ADT: 100 Docetaxel: 2 ARPI: 7
Chemotherapy monotherapy								
CALGB9182, 1999	Rx: Mitoxantrone + Hydrocortisone Ctrl: Hydrocortisone	232/ 242	10/01/1992- 09/01/1995	NA	OS	12.3 vs. 12.6 NA	3.7 vs. 2.3 § NA	ADT: 100
FIRSTANA, 2017	Rx1: Cabazitaxel20 Rx2: Cabazitaxel25 Ctrl: Docetaxel	1170/ 1168	05/01/2011- 04/01/2013	NA	OS	Rx1 vs. Ctrl: 24.5 vs. 24.3 Rx2 vs. Ctrl: 25.2 vs. 24.3	Rx1 vs. Ctrl: 13.4 vs. 12.1 § Rx2 vs. Ctrl: 13.1 vs. 12.1 §	ADT: 100 ARPI: 2

						Rx1 vs. Ctrl: 1.01 (0.85-1.20) Rx2 vs. Ctrl: 0.97 (0.82-1.16)	Rx1 vs. Ctrl: 0.92 (0.75-1.12) Rx2 vs. Ctrl: 0.96 (0.79-1.17)	
Kellokumpu-Lehtinen PL et al, 2013	Rx: Docetaxel (2W) Ctrl: Docetaxel	348/ 346	03/01/2004- 05/31/2009	18	TTF	19.5 vs. 17 1.40 (1.10-1.80)	15.8 vs. 14.6 ‖ 1.30 (1.00-1.60)	ADT: 100
Berry W et al, 2002	Rx: Mitoxantrone Ctrl: Placebo	120/ 119	03/01/1997- 01/01/1999	21.8	TTF	23 vs. 19 NA	Not reported	ADT: 100
Abratt RP et al, 2004	Rx: Vinorelbine + Hydrocortisone Ctrl: Hydrocortisone	362/ 414	04/01/1997- 08/01/2001	Rx: 24; Ctrl: 24.6	PFS	14.7 vs. 15.2 NA	3.7 vs. 2.8 ¶ NA	ADT: 100
PRINCE, 2018	Rx: Docetaxel (int) Ctrl: Docetaxel	424/ 187	08/01/2005- 05/01/2008	Rx: 26.8; Ctrl: 33.8	1-yr survival rates	18.3 vs. 19.3 1.14 (0.75-1.72)	10 vs. 5.4 ¶ 0.69 (0.43-1.05)	ADT: 100
TAX327, 2004	Rx1: Docetaxel Rx2: Docetaxel30 (W) Ctrl: Mitoxantrone	1002/ 1006	03/01/2000- 06/01/2002	Rx1: 20.7 Rx2: 20.7 Ctrl: 20.8	OS	Rx1 vs. Ctrl: 19.2 vs. 16.3 Rx2 vs. Ctrl: 17.8 vs. 16.3 Rx1 vs. Ctrl: 0.79 (0.67-0.93) † Rx2 vs. Ctrl: 0.87 (0.74-1.02)	Not reported	ADT: 100
Chemotherapy+ASO								
SYNERGY, 2017	Rx: Docetaxel + Custirsen Ctrl: Docetaxel	1000/ 1022	12/10/2010- 11/07/2012	Rx: 20.4; Ctrl: 21.7	OS	23.4 vs. 22 0.93 (0.79-1.10)	Not reported	ADT: 100 ARPI: 3
Chemotherapy+Chemotherapy								
SWOG-99-16, 2004	Rx: Docetaxel60 + Estramustine Ctrl: Mitoxantrone	620/ 770	10/01/1999- 01/01/2003	32	OS	17.5 vs. 15.6 0.80 (0.67-0.97) †	6.3 vs. 3.2 ¶ NA	ADT: 100
Chemotherapy+DES								
ECOG 3882 2003	Rx: Doxorubicin + DES Ctrl: Doxorubicin	80/ 150	04/01/1983- 06/01/1986	NA	OS	8.5 vs. 7.7 NA	Not reported	ADT: 100
Chemotherapy+ERA								
ENTHUSE (M1c), 2013	Rx: Docetaxel + Zibotentan Ctrl: Docetaxel	1044/ 1052	01/24/2008- 05/10/2011	NA	OS	20 vs. 19.2 1.00 (0.84-1.18)	NA 1.00 (0.87-1.14) ¶	ADT: 100
SWOG S0421,	Rx: Docetaxel	930/	08/01/2006-	NA	OS;	17.8 vs. 17.6	9.2 vs. 9.1 §	ADT: 100

2013	+ Atrasentan Ctrl: Docetaxel	1038	05/01/2010		PFS	1.04 (0.90-1.19)	1.02 (0.89-1.16)	
Chemotherapy+IMiD								
MAINSAIL, 2015	Rx: Docetaxel + Lenalidomide Ctrl: Docetaxel	1015/ 1059	11/11/2009- 11/23/2011	8	OS	17.7 vs. NR 1.53 (1.17-2.00)	10.4 vs. 10.6 [§] 1.32 (1.05-1.66)	ADT: 100
Chemotherapy+PDGFRi								
Mathew P et al, 2007	Rx: Docetaxel30 (W) + Imatinib Ctrl: Docetaxel30 (W)	144/ 116	04/01/2003- 07/01/2005	NA	PFS	20.9 vs. NR 1.67 (0.77-3.64)	4.2 vs. 4.2 [¶] NA	ADT: 100
Chemotherapy+TKI								
READY, 2013	Rx: Docetaxel + Dasatinib Ctrl: Docetaxel	1380/ 1522	10/30/2008- 04/11/2011	19	OS	21.5 vs. 21.2 0.99 (0.87-1.13)	11.8 vs. 11.1 [¶] 0.92 (0.82-1.05)	ADT: 100
Chemotherapy+VEGFi								
CALGB 90401, 2012	Rx: Docetaxel + Bevacizumab Ctrl: Docetaxel	1050/ 1050	05/01/2005- 12/01/2007	NA	OS	22.6 vs. 21.5 0.91 (0.70-1.05)	9.9 vs. 7.5 [§] 0.80 (0.71-0.91)	ADT: 100
VENICE, 2013	Rx: Docetaxel+ Aflibercept Ctrl: Docetaxel	1200/ 1224	08/17/2007- 02/11/2010	35	OS	22.1 vs. 21.2 0.94 (0.82-1.08)	6.9 vs. 6.2 [¶] NA	ADT: 100
Chemotherapy+VitD-Analog								
ASCENT2, 2011	Rx: Docetaxel + Calcitriol Ctrl: Docetaxel	1200/ 953	02/09/2006- 11/02/2007	11.7	OS	17.8 vs. 20.2 NA	Not reported	ADT: 100
ERA monotherapy								
ENTHUSE (PF), 2012	Rx: Zibotentan Ctrl: Placebo	580/ 594	11/20/2007- 02/13/2009	NA	OS	24.5 vs. 22.5 0.87 (0.69-1.10)	6.2 vs. 6.5 [¶] 1.01 (0.85-1.21)	ADT: 100
Carducci MA et al, 2007	Rx: Atrasentan Ctrl: Placebo	Not specified/ 809	06/25/2001- 11/25/2002	NA	Time to disease progression	20.5 vs. 20.3 0.97 (0.81-1.17)	NA 0.89 (0.76-1.04) [‖]	ADT: 100
IMiD monotherapy								
Sternberg C et al, 2016	Rx: Tasquinimod Ctrl: Placebo	1200/ 1245	03/29/2011- 12/07/2012	Rx: 30; Ctrl: 30.7	rPFS	21.3 vs. 24 1.01 (0.94-1.28)	7.0 vs. 4.4 [§] 0.64 (0.54-0.75)	ADT: 100 ARPI: 9
Immunotherapy monotherapy								
CA184-095, 2017	Rx: Ipilimumab Ctrl: Placebo	600/ 602	07/28/2010- 08/28/2015	NA	OS	28.7 vs. 29.7 1.11 (0.88-1.39)	5.6 vs. 3.8 [¶] 0.67 (0.55-0.81)	ADT: 100

D9901, 2006	Rx: Sipuleucel-T Ctrl: Placebo	120/ 127	01/01/2000- 10/01/2001	36	TTP	25.9 vs. 21.4 0.58 (0.39-0.88) †	11.7 vs. 9.1 ‖ 0.69 (0.47-1.01)	ADT: 100
D9902A, 2009	Rx: Sipuleucel-T Ctrl: Placebo	Not specified/ 98	05/01/2000- 03/01/2003	36	TTP	19 vs. 15.7 0.79 (0.48-1.28)	10.9 vs. 9.9 ‖ 0.92 (0.59-1.45)	ADT: 100
Immunotherapy+GMCSF								
PROSPECT, 2019	Rx1: PVAC + GMCSF Rx2: PVAC Ctrl: Placebo	1200/ 1297	11/01/2011- 07/01/2015	NA	OS	Rx1 vs. Ctrl: 33.2 vs. 34.3 Rx2 vs. Ctrl: 34.4 vs. 34.3 Rx1 vs. Ctrl: 1.02 (0.86-1.22) Rx2 vs. Ctrl: 1.01 (0.84-1.20)	Not reported	ADT: 100
PARPi+ARPI								
TALAPRO-2, 2023	Rx: Talazoparib + Enzalutamide Ctrl: Enzalutamide	750/ 805	01/07/2019- 09/17/2020	Rx: 24.6; Ctrl: 24.9	rPFS	45.8 vs. 37 0.80 (0.66-0.96) †	33.1 vs. 19.5 0.67 (0.55-0.81) §	ADT: 100 Docetaxel: 22 ARPI: 6
Phenylurea monotherapy								
Small EJ et al, 2000	Rx: Suramin Ctrl: Placebo	466/ 458	02/01/1994- 12/01/1996	NA	Pain, opioid analgesic use	9.4 vs. 9.2 NA	Not reported	ADT: 100

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; rPFS: radiographic progression-free survival; PFS: progression-free survival; ARPI: androgen-receptor pathway inhibitor; PI3K/AKTi: phosphatidylinositol 3-kinase and protein kinase B inhibitor; TTF: time to treatment failure; ASO: antisense oligonucleotide; DES: diethylstilbestrol diphosphate; IMiD: immunomodulatory drug; PDGFR: platelet-derived growth factor receptor; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor; VitD: vitamin d; ERA: endothelin receptor antagonist; PVAC: PROSTVAC (viral vector-based immunotherapy); SSE: symptomatic skeletal related event; GMCSF: granulocyte-macrophage colony-stimulating factor; PARPi: poly(ADP-ribose) polymerase inhibitor;

Note: Data for TALAPRO-2 stratified according to type of genetic alteration present is reported in Supplement Table 3. The color 'green' represents a positive trial, 'red' represents a negative trial.

* Assessed by blinded independent central review committee
† Statistically significant overall survival benefit was observed
‡ Assessed by investigator
§ Radiographic progression free survival
‖ Time to disease progression
¶ Composite progression free survival

Cabazitaxel20: Cabazitaxel 20 mg/m^2 IV on day 1 of every 3-week cycle
Cabazitaxel25: Cabazitaxel 25 mg/m^2 IV on day 1 of every 3-week cycle

Docetaxel (2W): Docetaxel 75 mg/m^2 IV on days 1 and 15 of a 4-week cycle
Docetaxel (int): Docetaxel 35 mg/m^2 IV on days 1, 8, 15, repeat cycle at day 29
Docetaxel30 (W): Docetaxel 30 mg/m^2 IV on days 1, 8, 15, 22 and 29 of a 6-week cycle
Remaining drugs were administered at standard doses

Table 2. Summary of characteristics and results of included phase III trials in which patients received prior ADT and ARPI

Trial	Arm	Estimated /Actual Accrual	Years of enrollment	Median follow up - months	Primary Endpoint	OS HR (95% CI)	PFS HR (95% CI)	Prior therapy | %
ARPI+ARPI								
PLATO, 2018	Rx: Enzalutamide + Abiraterone Ctrl: Abiraterone	250/ 251	10/22/2013 onwards	NA	PFS	Not reported	5.7 vs. 5.6 * 0.83 (0.61-1.12)	ADT: 100 ARPI: 100
ARPI+Immunotherapy								
IMbassador250, 2022	Rx: Enzalutamide + Atezolizumab Ctrl: Enzalutamide	Not specified/ 759	06/01/2017-05/01/2018	Rx: 15.2; Ctrl: 16.6	OS	15.9 vs. 20.5 1.58 (1.13-2.20)	4.2 vs. 4.4 † 0.98 (0.75-1.27)	ADT: 100 Docetaxel: 48 ARPI: 100
Chemotherapy+ARPI								
PRESIDE, 2022	Rx: Docetaxel + Enzalutamide Ctrl: Docetaxel	182/ 271	12/01/2014-02/15/2016	Rx: 6.3; Ctrl: 8.1	PFS	Not reported	9.5 vs. 8.3 * 0.72 (0.53-0.96)	ADT: 100 ARPI: 100
Chemotherapy+Immunotherapy								
KEYNOTE-921, 2025	Rx: Docetaxel + Pembrolizumab Ctrl: Docetaxel	1000/ 1030	05/30/2019-06/17/2021	22.7	OS, rPFS	19.6 vs. 19 0.92 (0.78-1.09)	8.6 vs. 8.3 0.85 (0.71-1.01)	ADT: 100 Docetaxel: 12 ARPI: 99
PARPi monotherapy								
TRITON-3, 2023	Rx: Rucaparib Ctrl: Enzalutamide /Abiraterone /Docetaxel	400/ 405	02/08/2017-02/02/2022	62	rPFS	*Overall population:* 23.6 vs. 20.9 0.94 (0.72-1.23) *Subgroup for physician's choice of ARPI:* 0.38 (0.25-0.58) ‡§ *Subgroup for physician's choice of Docetaxel:* 0.53 (0.37-0.77) ‡§	10.2 vs. 6.4 † 0.61 (0.47-0.80) 0.47 (0.34-0.66) 0.64 (0.46-0.88)	ADT: 100 Docetaxel: 22 ARPI: 100
PROfound, 2020	Rx: Olaparib Ctrl: Enzalutamide /Abiraterone	240/ 387	04/01/2017-11/01/2018	Rx: 5.4; Ctrl: 13.2	rPFS	NA 1.12 (0.69-1.85)	NA 0.77 (0.50-1.22) †	ADT: 100 Docetaxel: 65 ARPI: 100
Radioligand monotherapy								
PSMAfore, 2024	Rx: 177Lu Ctrl: Enzalutamide /Abiraterone	450/ 468	06/15/2021-10/07/2022	24.1	rPFS	23.7 vs. 23.9 0.98 (0.75-1.28)	11.6 vs. 5.6 † 0.49 (0.39-0.61)	ADT: 100 ARPI: 100

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; rPFS: radiographic progression-free survival; PFS: progression-free survival; ARPI: androgen-receptor pathway inhibitor; PARPi: poly (ADP-ribose) polymerase inhibitor; 177Lu: 177Lu-PSMA-617

Note: Data for TRITON-3 and PROfound stratified according to the type of genetic alteration present is reported in Supplement Table 4. The color 'green' represents a positive trial, 'red' represents a negative trial. Only PLATO was a phase IV trial; the rest were phase III.

* Composite progression free survival

† Radiographic progression free survival

‡ Statistically significant overall survival benefit was observed

§ Overall survival subgroup data according to physician's choice was only reported for the patients who had *BRCA* alterations

Table 3. Summary of characteristics and results of included phase III trials in which patients received prior ADT and Docetaxel

Trial	Arm	Estimated /Actual Accrual	Years of enrollment	Median follow up - months	Primary Endpoint	OS HR (95% CI)	PFS HR (95% CI)	Prior therapy | %
ARPI monotherapy								
AFFIRM, 2012	Rx: Enzalutamide Ctrl: Placebo	1170/ 1199	09/01/2009- 11/01/2010	14.4	OS	18.4 vs. 13.6 0.63 (0.53-0.75) *	8.3 vs. 2.9 † 0.40 (0.35-0.47)	ADT: 100 Docetaxel: 100
COU-AA-301, 2011	Rx: Abiraterone Ctrl: Placebo	1158/ 1195	05/01/2008- 07/01/2009	20.2	OS	15.8 vs. 11.2 0.74 (0.64-0.86) *	5.6 vs. 3.6 † 0.66 (0.58-0.76)	ADT: 100 Docetaxel: 100
ELM-PC 5, 2015	Rx: TAK-700 Ctrl: Placebo	1083/ 1099	11/15/2010 onwards	10.7	OS	17 vs. 15.2 0.89 (0.74-1.06)	8.3 vs. 5.7 † 0.76 (0.65-0.89)	ADT: 100 Docetaxel: 100
SAKK 08/11, 2016	Rx: TAK-700 Ctrl: Placebo	192/ 47	11/09/2012- 07/17/2014	Rx: 17; Ctrl: 18.4	EFS	Not reported	8.5 vs. 2.8 † 0.42 (0.20-0.91)	ADT: 100 Docetaxel: 100
Chemotherapy monotherapy								
PROSELICA, 2017	Rx: Cabazitaxel20 Ctrl: Cabazitaxel25	1200/ 1200	04/01/2011- 12/01/2013	NA	OS	NA 1.00 (0.86-1.15)	2.9 vs 3.5 ‡ 1.10 (0.97-1.24)	ADT: 100 Docetaxel: 100 ARPI: 27
TROPIC, 2010	Rx: Cabazitaxel25 Ctrl: Mitoxantrone	720/ 755	01/02/2007- 10/23/2008	12.8	OS	15.1 vs. 12.7 0.70 (0.59-0.83) *	2.8 vs. 1.4 ‡ 0.74 (0.64-0.86)	ADT: 100 Docetaxel: 100
Chemotherapy+ASO								
AFFINITY, 2017	Rx: Cabazitaxel25 + Custirsen Ctrl: Cabazitaxel25	630/635	09/09/2012- 09/29/2014	29.6	OS	14.1 vs. 13.4 0.95 (0.80-1.12)	Not reported	ADT: 100 Docetaxel: 100 ARPI: 59
TKI monotherapy								
SUN 1120, 2013	Rx: Sunitinib Placebo	819/ 873	07/01/2008- 08/01/2010	8.7	OS	13.1 vs. 11.8 0.91 (0.76-1.10)	5.6 vs. 4.1 † 0.730.59-0.89)	ADT: 100 Docetaxel: 100

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; PFS: progression-free survival; EFS: event free survival; ARPI: androgen-receptor pathway inhibitor; ASO: antisense oligonucleotide; TKI: tyrosine kinase inhibitor

Note: The color 'green' represents a positive trial, 'red' represents a negative trial.
* Statistically significant overall survival benefit was observed
† Radiographic progression free survival
‡ Composite progression free survival

Cabazitaxel20: Cabazitaxel 20 mg/m^2 IV on day 1 of every 3-week cycle
Cabazitaxel25: Cabazitaxel 25 mg/m^2 IV on day 1 of every 3-week cycle
Remaining drugs were administered at standard doses.

Table 4. Summary of characteristics and results of included phase III trials in which patients received prior ADT, ARPI and Docetaxel

Trial	Arm	Estimated /Actual Accrual	Years of enrollment	Median follow up - months	Primary Endpoint	OS HR (95% CI)	PFS HR (95% CI)	Prior therapy | %
Chemotherapy monotherapy								
CARD, 2019	Rx: Cabazitaxel25 Ctrl: Enzalutamide /Abiraterone	234/ 255	11/01/2015-11/01/2018	9.2	rPFS	13.6 vs. 11 0.64 (0.46-0.89) *	8 vs. 3.7 † 0.54 (0.40-0.73)	ADT: 100 Docetaxel: 100 ARPI: 99.6
PARPi+Immunotherapy								
KEYLYNK-010, 2023	Rx: Olaparib + Pembrolizumab Ctrl: Enzalutamide /Abiraterone	780/ 793	05/30/2019-07/16/2021	18.7	OS; rPFS	15.8 vs. 14.6 0.94 (0.77-1.14)	4.6 vs. 4.2 † 0.96 (0.79-1.16)	ADT: 100 Docetaxel: 98 ARPI: 100
Radioligand therapy+Standard of Care								
VISION, 2021	Rx: 177Lu + SOC Ctrl: SOC	814/ 831	06/04/2018-10/23/2019	20.9	OS; PFS	15.3 vs. 11.3 0.62 (0.52-0.74) *	8.7 vs. 3.4 † 0.40 (0.29-0.57)	ADT: 100 Docetaxel: 97 ARPI: 100
TKI monotherapy								
COMET-1, 2016	Rx: Cabozantinib Ctrl: Prednisone	Not specified/ 1028	07/02/2012-11/14/2014	NA	OS	11 vs. 9.8 0.90 (0.76-1.06)	5.6 vs. 2.8 † 0.48 (0.40-0.57)	ADT: 100 Docetaxel: 100 ARPI: 92 (Abi); 25 (Enza)

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; PFS: progression-free survival; rPFS: radiographic progression-free survival; ARPI: androgen-receptor pathway inhibitor; PARPi: poly (ADP-ribose) polymerase inhibitor; TKI: tyrosine kinase inhibitor; 177Lu: 177Lu-PSMA-617: SOC: standard of care; Abi: abiraterone; Enza: enzalutamide

Note: The color 'green' represents a positive trial, 'red' represents a negative trial. Only CARD was a phase IV trial; the rest were phase III.

Cabazitaxel25: Cabazitaxel 25 mg/m^2 IV on day 1 of every 3-week cycle
* Statistically significant overall survival benefit was observed
† Radiographic progression free survival

Table 5. Summary of characteristics and results of included phase III trials in which patients received heterogeneous prior therapy

Trial	Arm	Estimated /Actual Accrual	Years of enrollment	Median follow up - months	Primary Endpoint	OS HR (95% CI)	PFS HR (95% CI)	Prior therapy | %
Chemotherapy+Immunotherapy								
VIABLE, 2022	Rx: Docetaxel + DCVAC Ctrl: Docetaxel	1170/ 1182	06/01/2014-11/01/2017	NA	OS	23.9 vs. 24.3 1.04 (0.90-1.21)	11.1 vs. 11.1 * 0.99 (0.86-1.14)	ADT: 100 ARPI: 31

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; PFS: progression-free survival; ARPI: androgen-receptor pathway inhibitor

Note: The color 'green' represents a positive trial, 'red' represents a negative trial.
* Radiographic progression free survival

Table 6. Summary of characteristics and results of included phase III trials that reported data for multiple subgroups

Trial	Arm	Estimated /Actual Accrual	Years of enrollment	Median follow up - months	Primary Endpoint	OS HR (95% CI)	PFS HR (95% CI)	Prior therapy | %
Chemotherapy monotherapy								
SPARC, 2009	Rx: Satraplatin Ctrl: Placebo	912/ 950	09/01/2003- 01/01/2006	Rx: 6.7; Ctrl: 9	OS; PFS	*Prior ADT:* NA 1.03 (0.82-1.29) *Prior ADT+Docetaxel:* NA 0.91 (0.72-1.14) *Heterogeneous Prior Therapy:* 14.1 vs. 14.1 0.98 (0.84-1.15)	Not reported Not reported 2.6 vs. 2.2 * 0.67 (0.57-0.77)	ADT: 100 Docetaxel: 51
Immunotherapy monotherapy								
IMPACT, 2010	Rx: Sipuleucel-T Ctrl: Placebo	500/ 512	08/01/2003- 11/01/2007	34.1	OS	*Prior ADT:* NA 0.79 (0.59-1.03) *Prior ADT+Docetaxel:* NA 0.68 (0.35-1.24)	3.7 vs. 3.6 † 0.95 (0.77-1.17) Not reported	ADT: 100 Docetaxel: 14
PARPi+ARPI								
PROpel, 2023	Rx: Olaparib + Abiraterone Ctrl: Abiraterone	720/ 796	10/01/2018- 01/01/2020	Rx: 36.5; Ctrl: 36.6	rPFS	*Prior ADT:* NA 0.85 (0.67-1.07) *Prior ADT+Docetaxel:* NA 0.76 (0.52-1.11)	NA 0.62 (0.49-0.79) ‡ NA 0.66 (0.44-0.98) ‡	ADT: 100 Docetaxel: 24 ARPI: 0.1
MAGNITUDE, 2023	Rx: Niraparib + Abiraterone	400/ 423	05/01/2019- 03/01/2021	18.6	rPFS	*Prior ADT+ARPI:* Not reported	NA	ADT: 100 Docetaxel: 20

	Ctrl: Abiraterone						0.83 (0.48-1.42) ‡	ARPI: 26
						Prior ADT+Docetaxel:		
						Not reported	13.4 vs. 10.9 ‡ 0.89 (0.48-1.66)	
						Heterogeneous Prior Therapy:		
						NA	16.7 vs. 13.7 ‡	
						0.70 (0.49-0.99) §	0.76 (0.60-0.97)	
Radiopharmaceutical monotherapy								
ALSYMPCA, 2013	Rx: Radium-223 Ctrl: Placebo	900/ 921	06/01/2008-02/01/2011	36	OS	*Prior ADT:*		ADT: 100 Docetaxel: 57
						16.1 vs. 11.5 0.69 (0.52-0.92) §	Not reported	
						Prior ADT+Docetaxel:		
						14.4 vs. 11.3 0.70 (0.56-0.88) §	Not reported	
						Heterogeneous Prior Therapy:		
						14.9 vs. 11.3 0.70 (0.58-0.83) §	Not reported	

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; rPFS: radiographic progression-free survival; PFS: progression-free survival; ARPI: androgen-receptor pathway inhibitor; PARPi: poly (ADP-ribose) polymerase inhibitor

Note: Data for PROpel and MAGNITUDE stratified according to the type of genetic alteration present is reported in Supplement Table 3. The color 'green' represents a positive trial, 'red' represents a negative trial.

* Composite progression free survival

† Time to disease progression

‡ Radiographic progression free survival

§ Statistically significant overall survival benefit was observed

Table 7: Summary of Evidence

Prior ADT only			Prior ADT + ARPI			Prior ADT + Docetaxel			Prior ADT + ARPI + Docetaxel		
Treatment	**Trial**	**Evidence Category**	**Treatment**	**Trial**	**Evidence Category**	**Treatment**	**Trial**	**Evidence Category**	**Treatment**	**Trial**	**Evidence Category**
HRR positive											
BRCA positive											
PARPi + ARPI	*MAGNITUDE PROpel TALAPRO-2*	**Category B**	**PARPi**	*PROfound TRITON-3*	**Category B**	**PARPi + ARPI**	*MAGNITUDE PROpel TALAPRO-2*	**Category B**	**PARPi**	*PROfound TRITON-3*	**Category B**
BRCA negative *											
PARPi + ARPI	*MAGNITUDE PROpel TALAPRO-2*	**Category B**	**PARPi**	*PROfound*	**Category B**	**PARPi + ARPI**	*MAGNITUDE PROpel TALAPRO-2*	**Category B**	**PARPi**	*PROfound*	**Category B**
HRR negative											
Abiraterone +Prednisone	*COU-AA-302*	**Category A**	**Docetaxel**	*TAX327*	**Category B**	**Abiraterone +Prednisone**	*COU-AA-301*	**Category A**	**Cabazitaxel**	*CARD*	**Category B**
Enzalutamide	*PREVAIL*	**Category A**	**Cabazitaxel** †	*FIRSTANA*	**Category B**	**Enzalutamide**	*AFFIRM*	**Category A**			
Docetaxel	*TAX327*	**Category A**				**Cabazitaxel**	*TROPIC*	**Category A**			
Cabazitaxel †	*FIRSTANA*	**Category B**									
PSMA+											
-	-	-	-	-	-	-	-	-	**177LuPSMA 617**	*VISION*	**Category B**
Bone only, symptomatic											
Radium-223	*ALSYMPCA*	**Category B**	**Radium-223**	*ALSYMPCA*	**Category B**	**Radium-223**	*ALSYMPCA*	**Category B**	**Radium-223**	*ALSYMPCA*	**Category B**
Indolent disease (slow rising PSA, asymptomatic/low volume disease)											
Sipuleucel-T	*D9901 D9902A IMPACT*	**Category B**	**Sipuleucel-T**	*D9901 D9902A IMPACT*	**Category B**	**Sipuleucel-T**	*D9901 D9902A IMPACT*	**Category B**	**Sipuleucel-T**	*D9901 D9902A IMPACT*	**Category B**
MSI-high/dMMR											
Pembrolizumab	*KEYNOTE-158*	**Category C**	**Pembrolizumab**	*KEYNOTE-158*	**Category C**	**Pembrolizumab**	*KEYNOTE-158*	**Category C**	**Pembrolizumab**	*KEYNOTE-158*	**Category C**
Oligometastatic disease/ progression											

Radiotherapy/ Surgery	*ARTO*	**Category C**	**Radiotherapy/ Surgery**	*ARTO*	**Category C**	**Radiotherapy/ Surgery**	*ARTO*	**Category C**	**Radiotherapy/ Surgery**	*ARTO*	**Category C**
Disease Progression despite all above options											
-	-	-	-	-	-	-	-	-	**Cabazitaxel +Carboplatin**	*MDACC Study*	**Category C**
									Carboplatin	-	**Category C**
									Best supportive/ palliative care	-	**Category C**

Category A: Direct evidence from a randomized phase III clinical trial available
Category B: Consensus of panel of oncologists with extrapolated evidence from available randomized phase III clinical trials
Category C: Consensus of panel of oncologists without existing phase III evidence

Abbreviations: ADT: androgen deprivation therapy; PARPi: poly (ADP-ribose) polymerase inhibitor; ARPI: androgen-receptor pathway inhibitor; MSI-high: microsatellite instability-high; dMMR: deficient mismatch repair

Note: ARTO [199] and KEYNOTE-158 [200] were phase II trials that were not included in this systematic review because they did not meet the prespecified inclusion criteria. However, due to the lack of available trials for mCRPC patients with MSI-high/dMMR or oligometastatic disease progression, these trials were used to inform the recommendations based on the consensus of a panel of oncologists.

* The greatest benefit in patients with non-*BRCA HRR* alterations were observed in those having alterations in *CDK12* and *PALB2* genes with limited benefit observed in *ATM* and *CHEK2* genes. PARPi + ARPI options include Niraparib + Abiraterone, Olaparib + Abiraterone, and Talazoparib + Enzalutamide. PARPi monotherapy options include Olaparib, and Rucaparib

† Cabazitaxel is an alternative option for docetaxel in patients who have experienced an allergic reaction or toxicity like peripheral neuropathy

Figure 1. PRISMA flowchart outlining the study selection process