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Original Article

EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Part II—2026 Update: Treatment of Relapsing and Metastatic Prostate Cancer

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Abstract

Background and objective: To present a summary of the 2026 version of the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy & Oncology (ESTRO)-European Society of

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Urogenital Radiology (ESUR)-International Society of Urological Pathology (ISUP)-International Society of Geriatric Oncology (SIOG) Guidelines on the treatment of relapsing, metastatic hormone-sensitive and castration-resistant prostate cancer (PCa).

Methods: The Panel performed a literature review of new data, covering the time frame between 2023 and 2025. The Guidelines were updated and a strength rating for each recommendation was added based on a systematic review of the evidence.

Key findings and limitations: Risk stratification for relapsing PCa after primary therapy may guide salvage therapy decisions. The range of treatment options for metastatic PCa has broadened, including androgen receptor pathway inhibitors (ARPI), metastasis-directed therapy, PARP inhibitors and their combinations, as well as PSMA-based therapy. The recommendations in the EAU Guidelines are based on clinical evidence and do not account for variations in cost, reimbursement structures, or resource availability across healthcare systems.

Conclusions and clinical implications: The evidence in the field of relapsing, metastatic, and castration-resistant PCa is evolving rapidly. These PCa Guidelines reflect the multidisciplinary nature of PCa management. A full version is available from the EAU Guidelines Office or online (http://uroweb.org/guideline/ prostate-cancer/).

ADVANCING PRACTICE

What does this study add?
The 2026 EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on PCa summarise the most recent findings and advice for the implementation of data driven clinical practice.

Patient Summary
This article summarises the 2026 Guidelines for the treatment of relapsing, metastatic hormone-sensitive, and castration-resistant PCa. These Guidelines are evidence-based and guide the clinician in the discussion with the patient on the treatment decisions to be taken. The Guidelines are updated every year.

1. Introduction

A prior summary of the European Association of Urology (EAU) Guidelines on prostate cancer (PCa) was published in 2024 [1]. This paper summarises the 2026 version of the Guidelines on the treatment of relapsing, metastatic hormone-sensitive, and castration-resistant PCa. The Guidelines on screening, diagnosis and treatment of clinically localised and locally advanced PCa are published in a separate paper [2]. To facilitate evaluation of the quality of the information provided, a strength rating form has been completed for each recommendation.

2. Methodology

For the 2026 update of the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy & Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Urological Pathology (ISUP)-International Society of Geriatric Oncology (SIOG) Guidelines on Prostate Cancer, new evidence was identified, collated and appraised through a structured assessment of the literature. Databases searched included Medline, EMBASE, and the Cochrane Libraries. Detailed search strategies are available on the on the EAU website: https://uroweb.org/guidelines/prostate-cancer/publications-appendices. Recommendations within the Guidelines were developed by the Panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. Strong recommendations are made when evidence quality is high and/or there is a favourable balance of benefits to harms and patient preferences. Weak recommendations are made when the evidence is of lower quality and/or benefits and patient preferences are less clear [3]. The recommendations in the EAU Guidelines are based on clinical evidence and do not account for variations in cost, reimbursement structures, or resource availability across healthcare systems.

3. Diagnosis and treatment of relapse after curative therapies

Guidelines for second-line therapy after treatment with curative intent are summarized in Table 2.

Table 1 – Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy versus salvage radiotherapy alone

Study	n	Risk groups	Median FU (mo.)	Regimen	Outcome	
GETUG-AFU 16 2019 [43]	369 SRT + ADT 374 RT	ISUP GG ≤ 2/3 89% SUP GG ≥ 4 11% cN0	112	66 Gy PBRT+ 6 mo. LHRH analogue 66 Gy PBRT	10 yr. PFS: RT + ADT, 64% PFS: RT, 49% p < 0.0001	MFS: RT + ADT, 75% MFS: RT, 69% p = 0.034
RTOG 9601 2017 [35]	384 SRT + ADT 376 SRT	pT2 R1, pT3 cN0	156	64.8 Gy PBRT + bicalutamide 24 mo. 64.8 Gy PBRT + placebo	12 yr. cumulative DM RT + ADT: 14% RT + placebo: 23% p = 0.005 OS RT + ADT: 76% RT + placebo: 71% p = 0.04	DSM RT + ADT: 5.8% RT + placebo: 13.4% p < 0.001
NRG Oncology/RTOG 0534 SPPORT [44]	564 SRT 578 SRT + ADT 574 SRT + PBRT + ADT	pT2 or pT3 ISUP GG <5 Pre SRT PSA: 0.1–2.0	survivors: 8.2 years	64.8–0.2 Gy PBRT 64.8–70.2 Gy PBRT 6 mo. LHRH analogue 64.8–70.2 Gy PBRT + 45 Gy PLNRT 6 mo. LHRH analogue	5 yr. FFP (primary endpoint) 70.9% Group 1 81.3% Group 2 87.4% Group 3	Comparisons: G 3 vs. G 1: p < 0.0001 G 2 vs. G 1: p < 0.0001 G 3 vs. G 2: p < 0.0027
RADICALS HD 0 vs. 6 mo. ADT [39]	737 SRT 747 SRT+ADT	ISUP >7 (11%) ≥ pT3b (17%) R1 (62%) PSA: < 0.3 (61%) ≥ 0.5 (19%) R1 (62%) N1 (3%)	108	52.5 Gy, 20fx PBRT (29%) 66 Gy, 33fx PBRT (69%) LHRH analogue (83%)	10 yr. MFS: SRT: 79.2% SRT+ADT: 80.4% p = 0.71; HR: 0.89 CPFS: SRT: 68.3% SRT+ADT: 79.4% p = 0.071, HR:0.54	Max.GU-Tox G 3: SRT: 16% SRT+ADT: 13% p>0.05
RADICALS HD 6 versus 24 months ADT [40]	761 6 mo. ADT 762 24 mo. ADT	ISUP > 7 (29%) ≥ pT3b (31%) Med. Pre SRT PSA: 0.23 R1 (63%) N1 (8%)	107	52.5 Gy 20fx PBRT (19%) 66 Gy, 33fx PBRT (79%) LHRH analogue (84%)	10 yr. MFS: SRT+6 mo.: 71.9% SRT+24 mo.: 78.1% p = 0.029, HR: 0.77	Max.GU-Tox G3: SRT+6 mo.: 14% SRT+24 mo.:20% p = 0.025

ADT = androgen deprivation therapy; CPFS = clinical progression free survival; DM = distant metastasis; DSM = disease-specific mortality; FFP = freedom from progression; FU = follow-up; LHRH = luteinising hormone-releasing hormone; MFS = metastasis-free survival; mo. = months; n = number of patients; OS = overall survival; PBRT = prostate bed radiotherapy; PFS = progression-free survival; PLNRT = pelvic lymph node radiotherapy; RT = radiotherapy; yr. = years.

Table 2 – Recommendations for second-line therapy after treatment with curative intent

Recommendations for local salvage treatment	Strength rating
Biochemical recurrence (BCR) after radical prostatectomy	
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive prostate-specific antigen (PSA) rises.	Strong
Offer monitoring, including PSA, to EAU low-risk BCR patients.	Weak
Do not wait for a PSA threshold before starting treatment. Once the decision for salvage radiotherapy (SRT) has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with BCR.	Weak
Follow-up after radical prostatectomy or radiotherapy	
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and serum PSA measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong
BCR after radiotherapy	
Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
Offer highly selected patients with biopsy-proven local recurrence salvage radical prostatectomy, brachytherapy, stereotactic body radiotherapy in experienced centres.	Strong
Offer highly selected patients with biopsy-proven local recurrence high-intensity focused ultrasound, or cryosurgical ablation within a clinical trial setting or well-designed prospective cohort study.	Weak
Systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling time > 12 months.	Strong
Offer enzalutamide with androgen deprivation therapy to EMBARK-like patients (M0 patients on conventional imaging and PSA doubling time of ≤ nine months).	Strong

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3.1. Imaging in case of biochemical recurrence

In patients with biochemical recurrence (BCR), imaging can detect both local recurrences and distant metastases, however, the sensitivity of detection depends on the prostate-specific antigen (PSA) level. After radical prostatectomy (RP), prostate-specific membrane antigen (PSMA) hybrid imaging is the modality with the highest sensitivity at low PSA levels (< 0.5 ng/mL) and may help distinguishing patients with recurrences confined to the prostatic fossa from those with distant metastases, which may impact the design and use of post-RP salvage radiotherapy (SRT). After radiotherapy (RT), magnetic resonance imaging (MRI) has shown excellent results at detecting local recurrences and guiding prostate biopsy. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences and who are fit for these salvage therapies.

3.1.1. Prostate-specific membrane antigen hybrid imaging

Radiolabelled PSMA hybrid imaging has shown good potential in patients with BCR. The diagnostic performance of radiolabelled PSMA PET/CT in patients with BCR has been investigated in several systematic reviews and meta-analyses. The pooled sensitivity, specificity and AUC values for ^{18}F-PSMA PET/CT in the diagnosis of prostate recurrence and/or metastasis were 0.93 (0.89–0.95), 0.94 (0.85–0.98) and 0.96 (0.94–0.98), respectively. The per-patient pooled sensitivity and specificity values were 0.92 (0.86–0.96) and 0.83 (0.41–0.97), respectively. The per-lesion pooled sensitivity and specificity values were identical: 0.91 (0.86–0.94) [4]. The positivity rate increases with PSA, from 48% at PSA of 0.2–0.5 ng/mL to >90% at PSA >2 mL [5].

A prospective multicentre, multi-reader, open-label, phase II/III trial (OSPREY) evaluated the diagnostic performance of ^{18}F-DCFPyL in patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging [6]. Median sensitivity and median positive predictive value (PPV) were 95.8% (95% confidence interval [CI]: 87.8–99.0%) and 81.9% (95% CI: 73.7–90.2%), respectively.

Another prospective study evaluated the diagnostic performance of ^{18}F-DCFPyL in 208 men with BCR after RP or RT. The primary endpoint, the correct localisation rate was achieved, demonstrating positive findings on ^{18}F-DCFPyL PET/CT in the setting of negative standard conventional imaging [7]. At present, there are no conclusive data concerning the comparison of such tracers [8].

3.1.2. Imaging of local recurrence

MRI can detect local recurrences in the prostatic bed. The PSA threshold for MRI positivity appears to be between 0.3 and 0.5 ng/mL, and PSA kinetics also influence the MRI positivity, even at low PSA values [9]. Two single-centre studies found that a negative MRI was an independent predictor of failure of SRT [10,11]. Conversely, a small ($\leq$ 0.4 cc) relapse located at the vesico-urethral anastomosis is associated with excellent prognosis following SRT [12]. The Prostate Imaging for Recurrence Reporting (PI-RR) system has been recently launched to standardise MRI interpretation in the context of BCR after RP or RT [13]. Initial assessment suggests good reproducibility of the score [14,15].

The detection rates of ^{68}Ga-PSMA PET/CT in patients with BCR after RP increase with the PSA level [16]. Studies of PSMA PET/CT showed that a substantial part of recurrences after RP were located outside the prostatic fossa, even at low PSA levels [17,18]. Combining ^{68}Ga-PSMA PET and MRI may improve the detection of local recurrences as compared to ^{68}Ga-PSMA PET/CT alone [19–21].

In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained at least 24 months after initial treatment. Given the morbidity of local salvage options, histological proof of the local recurrence must be obtained before treating the patient [22].

MRI has yielded excellent results in identifying local recurrence and can be used for biopsy targeting and guiding local salvage treatment [22–24], even if it slightly underestimates the volume of the local recurrence [25]. PMSA PET/CT can also detect local recurrences after RT [26] and concordance between PSMA PET/CT and MRI is highly suggestive of cancer recurrence [27].

In the FLAME trial PSMA PET/CT was used for recurrence after RT. Intra-prostatic recurrences in intermediate- and high-risk patients appeared at the location of the primary tumour in 98% of cases [28].

3.2. Treatment of PSA-only recurrences after radical prostatectomy

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al.* reported a 75% reduced risk of systemic progression with SRT when comparing 856 SRT patients with 1801 non-SRT patients [29]. The RAVES and RADICALS trials assessing SRT in post-RP patients with PSA levels exceeding 0.1–0.2 ng/mL showed five-year freedom from BCR and BCR-free survival rates of 88% [30,31].

The PSA level at BCR was shown to be prognostic [29]. In a retrospective multicentre study including 25,551 patients with at most one high-risk factor after RP (ISUP GG 4–5 or pT3/4), initiating SRT above a PSA level of 0.25 ng/mL was associated with increased all-cause mortality (ACM) risk. After a median follow-up of six years, patients who received SRT at a PSA level > 0.25 ng/mL had a significantly higher ACM risk (adjusted hazard ratio [AHR]: 1.49; 95% CI: 1.11 to 2.00; p = 0.008) compared with patients who received SRT when the PSA was $\leq$ 0.25 mg/mL [32].

The EAU BCR definitions for low- and high-risk categories have been externally validated and may be helpful for individualised treatment decisions [33,34]. For men with limited life expectancy, salvage options are not indicated. A ‘wait and see‘ strategy is an option for the EAU BCR ‘Low-Risk’ group [33,34].

Optimal use of ADT with SRT remains unclear. Due to methodological discrepancies and also related to follow-up and risk, it is, as yet, not evident which patients should receive ADT, which type of ADT, and for how long. Men at high risk of further progression (e.g., with a PSA $\geq$ 0.7 ng/mL and GS $\geq$ 8) may benefit from SRT combined with two years of ADT. For those at lower risk (e.g., PSA < 0.7 ng/mL

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and GS = 8), SRT combined with six months of ADT may be sufficient [35]. Men with a low risk profile (PSA < 0.5 ng/mL and GS < 8) may receive SRT alone. In an unplanned subgroup analysis (RTOG 96-01) of men with a PSA of 0.61 to 1.5 (n = 253), an OS benefit was associated with antiandrogen assignment (HR: 0.61, 95% CI: 0.39–0.94) [36]. In those receiving early SRT (PSA < 0.6 ng/mL, n = 389), there was no improvement in OS (HR: 1.16, 95% CI: 0.79–1.70), with increased other-cause mortality (sub-distribution HR: 1.94, 95% CI: 1.17–3.20, p = 0.01) and increased odds of late grades 3–5 cardiac and neurologic toxic side effects (OR: 3.57, 95% CI: 1.09–15.97, p = 0.05). These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of antiandrogen treatment with SRT.

An SR addressing the benefit from combining ADT with SRT suggested risk stratification of patients based on the pre-SRT PSA (< 0.5, 0.6–1, > 1 ng/mL), margin status and ISUP GG as a framework to individualise treatment [37]. In addition, potential risk factors that should be considered are short PSA-doubling time and pT3b-4 tumours [38–42].

Differing results of three RCTs for additional short-term ADT (six months) to SRT are seen. One of the RCTs showed an increase of MFS [43], while the second and third RCTs did not [40,44]. Of two RCTs with long-term ADT in addition to SRT, one RCT showed a significant better OS [35] while the second did not [40], but this second RCT showed a moderate increase in MFS, at the cost of a higher rate of severe side effects. Additionally, in RADICALS HD, no subgroup analysis of risk factors was carried out. These conclusions were supported by the DADSPORT meta-analysis [45]. There is a suggestion that absolute benefits of ADT vary by prognostic risk and the number of prognostic risk factors in individual patients, especially in an early salvage setting (PSA $\leq$ 0.5 ng/mL). The potential for a greater benefit of long- over short-course HT seems to be small and must be weighed against increased toxicity and reduced QoL.

RCTs comparing SRT combined with ADT versus SRT alone are summarized in Table 1.

3.3. Treatment of PSA-only recurrences after radiation therapy

Therapeutic options in these patients are ADT or salvage local procedures, as well as a 'wait and see' approach, based on EAU BCR risk categories at relapse. A systematic review and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage high-intensity focussed ultrasound (HIFU), salvage cryotherapy, stereotactic body RT (SBRT), salvage low-dose rate (LDR) brachytherapy (BT), and salvage high-dose rate (HDR) BT in the management of locally recurrent PCa after primary radical external beam RT (EBRT) [46]. The outcomes were BCR-free survival at two and five years. No significant differences with regards to recurrence-free survival (RFS) between these modalities was found. Five-year RFS ranged from 50% after cryotherapy to 60% after HDR BT and SBRT. The authors reported that severe genitourinary (GU) toxicity exceeded 21% for whole-gland HIFU and RP, whereas it ranged from 4.2% to 8.1% with reirradiation. Differences in severe gastrointestinal (GI) toxicity also appeared to favour re-irradiation, particularly HDR BT [46]. Due to the methodological limitations of this review (the majority of the studies included were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes), the available evidence for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made.

3.4. Hormonal therapy for relapsing patients

A three-arm randomised phase III trial (EMBARK) evaluated response in patients with PCa who had high-risk BCR defined as a PSA doubling time (PSA-DT) of $\leq$ nine months and a PSA level of $\geq$ 2 ng/mL above the nadir after radiation therapy or $\geq$ 1 ng/mL after RP with or without postoperative RT [47]. Patients were randomly assigned 1:1:1 to receive enzalutamide daily plus leuprolide every 12 weeks (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group). The primary end point was MFS, as assessed by blinded independent central review, in the combination group as compared with the leuprolide-alone group. A key secondary end point was MFS in the monotherapy group as compared with the leuprolide-alone group. Other secondary end points were patient-reported outcomes and safety. A total of 1068 patients were randomised. After a median follow-up of 60.7 months, the five-year MFS was 87.3% (95% CI: 83.0–90.6) in the combination group, 71.4% (95% CI: 65.7–76.3) in the leuprolide-alone group, and 80.0% (95% CI: 75.0–84.1) in the monotherapy group. The combination of enzalutamide plus leuprolide was superior to leuprolide alone with regards to the MFS (hazard ratio [HR]: 0.42; 95% CI: 0.30–0.61; p < 0.001). Enzalutamide monotherapy also showed a superior MFS compared to leuprolide alone (HR: 0.63; 95% CI: 0.46–0.87; p = 0.005).

The 2025 update of this study presented eight-year OS. In the combination group, the OS was 78.9% (95% CI: 73.9–83.1) and 69.5% (95% CI: 64.0–74.3) in the leuprolide-alone group; the HR for death was 0.60 (95% CI: 0.44–0.80; p < 0.001) [48]. The eight-year OS with monotherapy was 73.1% (95% CI: 67.6–77.9), which did not differ significantly from that with leuprolide alone (HR: 0.83; 95% CI: 0.63–1.10; p = 0.19). This led to the conclusion that OS was significantly longer with the combination of enzalutamide and leuprolide than with leuprolide alone among patients with PCa with high-risk BCR. Enzalutamide monotherapy was not superior to leuprolide alone in the analysis of OS. These findings support the use of enzalutamide with ADT in high-risk BCR patients with a PSA-DT $\leq$ 9 months and a PSA above predefined thresholds following local therapy [49].

4. Hormone-sensitive metastatic prostate cancer

Most available prospective data rely on the definition of M1 disease based on CT scan or MRI and bone scintigraphy. Modern, more accurate imaging is increasingly being applied in clinical practice; however, its influence on treatment and patient outcomes has not yet been validated in prospective RCTs.

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Recommendations for the first-line treatment of hormone-sensitive metastatic disease are summarized in Table 6.

4.1. Prostate-specific antigen response as a prognostic factor

Based on a large SWOG 9346 cohort, the PSA level after seven months of ADT was used to create three prognostic groups (Table 3) [50]. A PSA $\leq$ 0.2 ng/mL at seven months has been confirmed as a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study independent of the addition of docetaxel [51]. Similarly, reaching PSA levels of $\leq$ 0.1 ng/mL after six months were shown to be correlated with long-term outcomes in the LATITUDE study [52]. Also for patients treated with ADT and apalutamide, a deep PSA decline defined by $\geq$ 90% from baseline or to PSA $\leq$ 0.2 ng/mL at a landmark of three months was associated with longer OS [53] for patients. A systematic review and meta-analysis confirmed that PSA response following initiation of ADT plus ARPI is strongly associated with OS across all stages of advanced PCa, including metastatic hormone-sensitive PCa (mHSPC), non-metatastatic and metastatic castration resistant PCa ([nm/m]CRPC). Achieving undetectable PSA levels or PSA decline of $\geq$ 90% was consistently associated with prolonged OS, underscoring PSA response as a robust early prognostic biomarker, although its role as a surrogate endpoint for OS remains to be validated [54].

4.2. Molecular testing

Different techniques may be applied for molecular testing including immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH), and next generation sequencing (NGS) of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). Treatment should be based on predictive [55] and not prognostic genetic aberrations. Patients potentially eligible for treatment intensification should be offered somatic DNA sequencing using panel-based assays [55]. Genetic testing on circulating tumour DNA (ctDNA) is an alternative option and has been used in some trials. The FoundationOne® Liquid CDx, has been FDA approved [52]. For patients with metastatic disease and assay failure, germline testing is recommended to identify *BRCA 1/2* alterations.

4.3. Combination therapies

4.3.1. Combination with an ARPI alone (abiraterone, apalutamide, enzalutamide, rezvilutamide, darolutamide)

Two large RCTs (STAMPEDE, LATITUDE) assessed the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC [56–58]. Both trials showed a significant OS benefit. In LATITUDE, with only *de novo* high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [56]. The HR in STAMPEDE was very similar, with 0.63 (0.52–0.76) in the total patient population (metastatic and non-metastatic) and an HR of 0.61 in the subgroup of metastatic patients [57]. While only high-risk patients were included in the LATITUDE trial, a *post-hoc* analysis from STAMPEDE showed the same benefit whatever the risk or the volume category was [59].

All secondary objectives, such as progression-free survival (PFS), time to radiographic progression, time to pain, or time to chemotherapy, were in favour of the combination. Based on these data upfront AAP combined with ADT has become a standard option in men presenting *de novo* metastatic PCa.

In five large RCTs, the addition of androgen receptor (AR) antagonists to ADT in men with mHSPC was tested [60–62]. In ARCHES, the primary endpoint was radiographic PFS (rPFS) which was significantly improved for the combination of enzalutamide and ADT (HR: 0.39; 95% CI: 0.3–0.5). Approximately 36% of the patients had low-volume disease: approximately 25% had prior local therapy and 18% of the patients had received prior docetaxel. In the final prespecified analysis, the key secondary endpoint OS was significantly improved (HR: 0.66; 95% CI: 0.53–0.81) and a significant benefit for rPFS was maintained (HR: 0.63; 95% CI: 0.52–0.76) [63].

In ENZAMET, the primary endpoint was OS. The addition of enzalutamide to ADT in the first analysis improved (HR: 0.67; 95% CI: 0.52–0.86) compared to ADT plus a non-steroidal antiandrogen. Approximately half of the patients had concomitant docetaxel: about 40% had prior local therapy and about half of the patients had low-volume disease [61]. In a planned later analysis with a median follow-up of 68 months, the OS benefit of adding enzalutamide was maintained (HR: 0.7 95% CI: 0.58–0.84) (Table 4) [64].

In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. In the primary analysis, rPFS was significantly improved through the addition of apalutamide (HR: 0.48; 95% CI: 0.39–0.6). Overall survival at 24 months was improved for the combination (HR: 0.67; 95% CI: 0.51–0.89). In the final analysis, the HR for OS was 0.65 (0.53–0.79) without adjustment for crossover. In this trial, 16% of patients had prior local therapy, 37% had low-volume disease, and 11% received prior docetaxel [60,65]. A secondary analysis of the TITAN study found that nearly half of the patients developing subsequent radiographic progression had no concomitant PSA progression, suggesting that heavy reliance on PSA monitoring may be inadequate for assessing disease activity in this context [66].

In the CHART trial, ADT plus rezvilutamide was evaluated versus ADT plus bicalutamide in patients with high-volume *de novo* metastatic disease. Ninety percent of the patients were recruited in China. Overall survival and rPFS were co-primary endpoints. At the preplanned interim analysis, rezvilutamide significantly improved rPFS compared with bicalutamide (HR: 0.44; 95% CI: 0.33–0.58) and OS (HR: 0.58; 95% CI: 0.44–0.77) (Table 5) [67]. Patient reported outcomes, as assessed by FACT-P and BPI-SF, were superior in

Table 3 – Prognostic factors based on the SWOG 9346 study [50]

PSA after 7 months after start of ADT	Median survival on ADT monotherapy
< 0.2 ng/mL	75 months
0.2 $\leq$ 4 ng/mL	44 months
> 4 ng/mL	13 months

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Table 4 – Results from the ENZAMET and TITAN studies with OS as primary endpoint

	ENZAMET [62,64]		TITAN [60,65]	
	ADT+ older antagonist ± docetaxel (SOC)	ADT + enzalutamide ± docetaxel	ADT + placebo	ADT + apalutamide
N	562	563	527	525
Newly diagnosed M+	72.1%	72.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS; rPFS	
Median follow-up	68 mo.		30.4 mo.	
OS	5-year survival: 67% (ADT + enzalutamide) 57% (SOC)		2-year survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.70 (0.58–0.84)		0.67 (0.51–0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo. = months; N = number of patients; rPFS = radiographic progression-free survival; SOC = standard of care; yr. = years.

Table 5 – Results from the ARCHES, CHART and ARANOTE studies

	ARCHES [61,63]		CHART [67]		ARANOTE [69]	
	ADT ± docetaxel	ADT + enzalutamide± docetaxel	ADT + bicalutamide	ADT + rezvilutamide	ADT + darolutamide	ADT + placebo
N	576	574	328	326	448	223
Newly diagnosed M+	63%	70%	100%	100%	71.1%	75.3%
Low volume	35%	38%	0%	0%	29.4%	29.6%
Use of early docetaxel	18% (previous)	18% (previous)	0%	0%	0	0
Primary endpoint(s)	rPFS		OS; rPFS		rPFS	
Median follow-up	44.6 mo.		29.3 mo.		25.3 mo.	25.0 mo.
Median rPFS	38.9 mo.	49.8 mo.	Not reached	25.0 mo.	Not reached	25.0 mo.
HR (95% CI) for rPFS	0.63 (0.52–0.76)		0.46 (0.36–0.60)		0.54 (0.41–0.71)	
Median OS	Not reached		Not reached		Not reached	
HR (95% CI) for OS	0.66 (0.53–0.81): main secondary endpoint		0.58 (0.44–0.77)		0.78 (0.58 – 1.05)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo. = months; N = number of patients; OS = overall survival; rPFS = radiographic progression-free survival.

men receiving rezvilutamide compared to bicalutamide, delaying both deterioration of pain and the FACT-P functional status [68].

In ARANOTE, darolutamide plus ADT was randomised 2:1 versus placebo plus ADT. It proved to significantly improve rPFS, which was the primary endpoint (HR: 0.54; 95% CI: 0.41-0.71], with consistent benefits across subgroups, including high- and low-volume disease [69]. Adverse events (AEs) were similar in the two groups. Overall survival was not statistically different in the final analysis (HR: 0.81; 95% CI: 0.59–1.12) (Table 5) [69].

In summary, the addition of the new ARPIs significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients had *de novo* metastatic disease, but a proportion of patients had metachronous disease. The effect in the subgroup analyses seemed to be consistent and therefore, a combination should also be offered to men progressing after radical local therapy [64,70,71].

4.3.2. *Triplet therapy: ADT and chemotherapy +/- ARPI*

The addition of abiraterone to ADT and docetaxel improved rPFS and OS in the PEACE-1 trial [72,73]. The trial has a 2 × 2 factorial design and participants with *de novo* (synchronous) metastatic PCa were randomised to standard of care (SOC), which was ADT at the beginning of the trial ADT, later ADT plus docetaxel for six cycles (if chemotherapy-fit) versus SOC plus RT versus SOC plus abiraterone versus SOC plus RT plus abiraterone. Co-primary endpoints were rPFS and OS, which were both significantly improved in the total population. Also, in the group of patients who received ADT plus docetaxel as SOC (n = 710), both rPFS and OS were increased with a HR: 0.5 (0.34–0.71) and 0.75 (0.59–0.95), respectively.

In the ARASENS phase III trial, all patients received ADT and docetaxel for six cycles as SOC plus darolutamide or placebo [74]. A total of 1306 metastatic patients were included, 14% of them with relapsed disease after radical local treatment (metachronous). The primary endpoint was OS, and this was statistically significantly improved by the addition of darolutamide (HR: 0.68; 95% CI: 0.57–0.8).

In this trial the occurrence of AEs was similar in both arms. Of the included patients, 77% had high volume and 70% high-risk disease. In an unplanned subgroup analysis, the beneficial effect of adding darolutamide versus placebo for OS was seen in the patients with high-volume (HR:

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Table 6 – Recommendations for the first-line treatment of hormone-sensitive metastatic disease*

Recommendations	Strength rating
First-line treatment	
Discuss all patients with hormone-sensitive metastatic disease in a multidisciplinary team	Strong
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting luteinising hormone-releasing hormone (LHRH) agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
At the start of ADT, offer LHRH antagonists or orchiectomy to patients with impending clinical complications, such as spinal cord compression or bladder outlet obstruction.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy ($\geq$1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide or rezvilutamide to patients with M1 disease who are fit for the regimen.	Strong
Offer ADT combined with darolutamide to patients with M1 disease who are fit for the regimen	Weak
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Test patients for somatic or germline homologous recombination repair aberrations, since they may qualify for the addition of niraparib to ADT plus abiraterone in patients with M1 disease.	Weak
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study.	Strong
Supportive care	
Assess osteoporosis risk factors and perform a dual emission X-ray absorptiometry scan when commencing long-term ADT, to mitigate osseous complications.	Strong
Offer bone protection to avoid fractures in patients receiving combination treatment.	Strong
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates and monitor serum calcium.	Strong
Treat painful bone metastases early on with palliative measures, such as radiotherapy and adequate use of analgesics.	Strong
In patients with spinal cord compression, start immediate high-dose corticosteroids and assess for spinal surgery, potentially followed by radiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

* All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.

0.69; 0.57–0.82), with high-risk (HR: 0.71; 0.58–0.86) and with low-risk disease (HR: 0.62; 0.42–0.9); for the small subgroup of patients with low-volume disease the results were less clear regarding an OS benefit (HR: 0.68; 0.41–1.13) [75].

In both PEACE I and ARASENS, docetaxel and the ARPI were given concomitantly. In ENZAMET about 45% of patients received concurrent docetaxel, in TITAN and ARCHES, 11-18% of patients received prior docetaxel as a part of SOC [60–65].

4.3.3. *ADT and ARPI +/- PARPI (AMPLITUDE)*

The AMPLITUDE phase III trial (n = 696) evaluated the combination of the Poly (ADP-ribose) polymerase (PARP) inhibitor niraparib with AAP in patients with mHSPC with germline or somatic alterations in HRR genes, including BRCA1 or BRCA2 or at least one of seven other HRR genes [76]. The primary endpoint was met, with a significant improvement in rPFS observed in the BRCA subgroup (HR 0.52; 95% CI: 0.37–0.72) and in the intention-to-treat population (HR 0.63; 95% CI: 0.49–0.80).

The secondary endpoint of OS was immature (HR: 0.79) and showed a trend towards favouring niraparib. More grade 3–4 AEs were reported in the niraparib arm: 75% versus 59%, especially anaemia (29% vs. 4.6%), hypertension (26.5% vs. 18.4%) and the need of transfusion. The treatment was more likely to be discontinued in the niraparib arm where also one case of MDS was reported.

4.3.4. *ADT and ARPI +/- AKT inhibitor (CAPItello-281)*

The phase III RCT CAPItello-281 trial evaluated the addition of the AKT inhibitor capivasertib to standard therapy with abiraterone plus ADT in patients with *de novo PTEN* deficient mHSPC [77]. Central testing of 6003 pre-screened patients confirmed IHC $\geq$ 90% *PTEN* loss in 1519 (25.3%) assessed specimens. Of 1012 included patients, 507 were randomised to capivasertib plus abiraterone and 505 to placebo plus abiraterone, with both arms receiving concomitant prednisone/prednisolone and ADT.

The primary endpoint of rPFS was significantly improved by capivasertib versus placebo (median 33.2 vs. 25.7 months; HR: 0.81; 95% CI: 0.66–0.98, $p < 0.034$. The secondary endpoint of OS was still immature (HR: 0.90; 95% CI: 0.71–1.15, $p = 0.401$).

4.4. *Treatment selection and patient selection*

Selecting patients for triplets of either docetaxel, niraparib or capivasertib in addition to ADT and ARPI is challenging. The addition of docetaxel was not formally tested against ADT and ARPI. The addition of niraparib or capivasertib requires upfront molecular and IHC testing and has been shown to improve rPFS but still not OS.

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In men with *HRR* mutations, especially in those with *BRCA* 1 or 2 alterations, the addition of niraparib to ADT and abiraterone plus prednisolone appears to be an important new option for this poor prognostic group of patients.

The OS benefit of adding docetaxel to ADT and ARPI has not been studied directly, and ADT plus ARPI remains the SOC in patients with no documented deficiency of *HRR* or *PTEN*. However, *PTEN* transcriptomic inactivity, as assessed by NGS of RNA, revealed shorter OS on ADT and abiraterone, but not with ADT and docetaxel, suggesting a higher docetaxel benefit in men with *PTEN* inactive PCa [77]. Ideally, the transcriptomic *PTEN* activity should be known when counselling patients with mHSPC. Of note, IHC-based *PTEN* loss and transcriptomic *PTEN* inactivity were not well aligned, as 30% of those with *PTEN* positivity by IHC were classified as transcriptomically *PTEN* inactive.

For patients without the above-mentioned molecular aberrations several network meta-analyses of the published data have concluded that combination therapy is more efficient than ADT alone, but none of the doublet combination therapies have been convincingly proven to be superior to another [78–83]. In a systematic review and meta-analysis looking at association between age and efficacy of combination therapy, patients appeared to benefit from combination therapy irrespective of age [83]. Consequently, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on frailty assessment or non-cancer comorbidities).

Docetaxel as sole addition to ADT is no longer recommended in the majority of patients if an ARPI is available and there are no contra-indications to use one. The different ARPIs appear to be similar regarding efficacy, but differ regarding their toxicity profiles. The choice of an ARPI should be based on the individual patient's risk profile and comorbidities [84]. For patients with metachronous low-volume PCa, ARPI doublet therapies were ranked as potentially the most efficacious treatment option, and the expected outcomes were not significantly different from those achieved by triplet regimens; however, docetaxel adds toxicity [78].

The question whether triplet therapy, ADT plus ARPI plus six cycles of docetaxel, is superior to ADT and ARPI doublet therapy has been addressed by multiple systematic reviews and meta-analyses. The choice between triplet therapy and the ADT and ARPI doublet therapy should be discussed with *de novo* and/or high-volume/high-risk disease patients [81,85,86].

4.5. Treatment of the primary tumour in newly diagnosed metastatic disease

The first reported trial evaluating prostate RT in men with mHSPC was the HORRAD trial. In this study, 432 patients were randomised to ADT alone or ADT plus intensity-modulated RT with image-guided RT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]) and median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [87].

The STAMPEDE trial evaluated 2061 men with (mHSPC) who were randomised to ADT alone versus ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [88]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved and patients categorised as low or high volume. In the low-volume subgroup (n = 819), there was a significant OS benefit by the addition of prostate RT. This was confirmed by the latest analysis of long-term follow-up (median follow-up of 61 months [HR: 0.64 for OS benefit in the low-volume group]) [89].

The randomised phase-III PEACE-1 trial with a 2×2 factorial design (SOC, SOC + abiraterone, SOC + RT, and SOC + abiraterone + RT) demonstrated that adding prostate RT (total dose 74 Gy in 37 fractions) significantly prolonged the co-primary endpoint of PFS from 4.4 years to 7.5 years in the low-volume metastatic burden group treated with SOC + ARPI. Additionally, a significant delay in the time to castration resistance was observed, although there was no improvement in OS in this group [90].

PEACE-1 also reported a significant reduction in the incidence of serious GU events such as obstruction, bleeding, insertion of double-J stent and transurethral resection of the prostate for patients treated with local RT to the prostate. This was a secondary endpoint in the PEACE-1 study where the preventive effect of RT was observed both in the cohort of patients with low-volume metastatic disease (26% vs. 11%; delay in the time to first serious GU event $p = 0.0002$;) and the overall cohort (22.3% vs 12.2%; $p = 0.0001$) [90].

A network meta-analysis of ten RCTs, including PEACE-1, in a population with *de novo* mHSPC and no prior docetaxel use, did not reveal a significant OS benefit for the addition of RT to SOC plus ARPI versus SOC plus ARPI alone (HR: 0.76; 95% CI: 0.51–1.16) [91].

4.6. Metastasis-directed therapy in M1 patients

In patients relapsing after a local treatment, a metastases-directed therapy (MDT) has been proposed, with the aim to delay systemic treatment. The same rationale can be applied in men with a single or only few metastases at diagnosis, i.e. oligometastatic disease. The definition of oligometastatic PCa varies and depends strongly on the applied imaging [92].

Two phase II trials, STOMP and ORIOLE, randomized mHSPC patients with one to three metachronous metastases to MDT versus observation [93,94]. In ORIOLE, MDT improved PFS compared with observation [94]. In STOMP, MDT improved ADT-free survival [93]. In a combined update of both STOMP and ORIOLE, MDT was associated with improved PFS versus observation, but other secondary endpoints, such as rPFS, were not shown to be superior [95].

A phase II trial assessed the biochemical response after ^{18}F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as $\geq 50\%$ PSA decline, was 60%, including 22% of patients with complete biochemical response [96].

The randomised phase II EXTEND trial investigated whether MDT, when added to SOC systemic treatment, improved PFS when compared to SOC systemic treatment

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alone in oligometastatic PCa patients, with oligometastatic being defined as maximally five lesions. In total, 87 patients were randomised and the vast majority presented with one or two metastatic lesions. In total, 51 patients received ADT alone, while 36 patients also received ARPI. The addition of MDT significantly improved both PFS (15.8 months vs. not reached; HR: 0.25; $p < 0.001$) and eugonadal PFS (6.1 months vs. not reached; HR: 0.32; $p = 0.03$). This significant benefit was observed both in the patient group receiving ADT alone or ADT + ARPI [97]. In analogy, the SATURN trial, which included 28 oligo-recurrent metastatic PCa patients, looked at the PFS of adding dual ARPI and MDT to existing ADT. The median PFS in SATURN was 19.3 months, and 50% of the patients still had an undetectable PSA six months after testosterone recovery. While MDT-induced toxicity was very low, adding dual ARPI induced grade 3 toxicity in 20% of the patients [98].

Five-year outcomes of SBRT for oligometastatic PCa from the prospective TRANSFORM phase II trial have been reported [99]. In total, 199 men (stage M1a/b and/or N1) received SBRT and 76% were hormone-naïve at baseline. The primary endpoint was five-year treatment escalation free survival, defined as freedom from any new cancer therapy other than further SBRT for up to five lesions. Ninety-three percent had prior RP, 46% of the patients had stage N1 only, 76% were staged by PET-CT. The rate of five-year treatment escalation free survival was 21.7% (CI: 15.7–28.7%) overall. These data suggest that SBRT-based MDT may be an effective option for delaying systemic treatment escalation in highly selected patients.

The randomised phase II clinical trial (RADIOSA) investigated whether six months ADT added to SBRT versus SBRT alone for hormone-sensitive metachronous oligo-recurrent PCa would improve clinical PFS [100]. In total, 105 patients were randomised, 52 to SBRT alone and 53 to SBRT + ADT, three patients were lost to follow-up. With a median follow-up of 31 months, the clinical PFS was 15.1 months for the SBRT-group (95% CI: 12.4-22.8) versus 32.2 months for the SBRT + ADT group (22.4-not reached; HR: 0.43; 0.26–0.72; $p = 0.0010$). No grade > 2 late ADT- or SBRT-related toxicities were reported.

Currently there are no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SBRT) as a promising therapeutic approach that must still be considered as investigational until the results of ongoing RCTs are available [101,102]. The RT-related toxicity of MDT is low, with almost no grade ≥ 3 toxicity [103–105].

5. Metastatic castration-resistant prostate cancer

Recommendations for systemic treatments of castrate-resistant disease are summarized in Table 9.

5.1. Treatment decisions and sequence of available options

Approved agents for the treatment of mCRPC in Europe are docetaxel, AAP, enzalutamide, cabazitaxel, olaparib, niraparib/AAP, talazoparib/enzalutamide, radium-223 and lutetium (^{177}Lu) vipivotide tetraxetan. For nmCRPC, darolutamide and enzalutamide have been approved. In general, sequencing of ARPIs like abiraterone and enzalutamide is not recommended, particularly if the time of response to ADT and to the first ARPI was short ($\leq$ six to 12 months) and high-risk features of rapid progression are present [106–108].

The use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence is recommended and should be applied early enough when the patient is still fit for chemotherapy. This is supported by high-level evidence [106].

In case of a known *BRCA* alteration, the use of a PARP inhibitor should always be prioritised, as these patients harbour an adverse prognosis and do not respond well to most other treatments. Use of a PARP inhibitor significantly improves rPFS and OS in these patients [109–112].

5.2. First-line treatment of metastatic castration resistant prostate cancer (Table 7)

5.2.1. Combination with Docetaxel

So far, no combination with docetaxel has proven to be superior to docetaxel alone in unselected mCRPC patients, including the combination with the checkpoint inhibitor pembrolizumab [113].

5.2.2. Combinations with PARP inhibitors

Based on the suggestion that there is a synergistic antitumour effect when combining an ARPI with a PARP inhibitor, several such combination trials were conducted in first-line mCRPC patients without prior ARPI use, with different trial designs and different patient- and molecular panel selection.

5.2.2.1. Abiraterone/prednisone plus olaparib. A randomised double-blind, phase III trial (PROpel) of AAP plus olaparib (300 mg twice daily) or placebo in patients with mCRPC in the first-line setting was conducted [114,115]. Patients ($n = 796$) were randomly assigned 1:1 to study treatment regardless of homologous recombination repair gene mutation (*HRR*m) status which was retrospectively evaluated and determined by tumour tissue and ctDNA tests. The primary end point was imaging-based PFS (ibPFS) by investigator assessment. All patients were ARPI naïve; 24% were docetaxel pretreated. The result was significantly positive in favour of the combination with ibPFS of 24.8 versus 16.6 months (HR: 0.66; 95% CI: 0.54-0.81; $p = 0.001$). In the prespecified final analyses the key secondary endpoint OS had only 47.9% maturity and did not meet the prespecified two-sided boundary for significance (HR: 0.81; 95% CI: 0.67−1.0; $p = 0.054$). The exploratory analysis of the subgroup of patients with positive HRRm status showed a rPFS HR of 0.50 (CI: 0.34–0.73). The BRCA mutated patients (11% of the intention to treat [ITT] population) had an even larger benefit for rPFS (HR: 0.24; 95% CI: 0.12–0.45) and the OS HR in these patients was 0.30 (95% CI: 0.15–0.59), suggesting that the overall benefit observed in the ITT population was primarily driven by patients with a BRCA mutation [116].

The most common AEs in patients receiving olaparib plus AAP were anaemia (48%; $\geq$ G3 15%), fatigue (38%), nausea (30%), diarrhoea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%) [116]. The combination of olaparib plus AAP was approved by

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Table 7 – Phase III randomised controlled trials - first-line treatment of mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [132]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		**OS: 17.52 vs. 15.6 mo.** (p = 0.02, HR: 0.80; 95% CI: 0.67–0.97) **PFS: 6.3 vs. 3.2 mo.** (p < 0.001)
TAX 327 2004, 2008 [133,134]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, prednisone 5 mg BID		**OS: 19.2 for 3-weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.** (p = 0.004, HR: 0.79, 95% CI: 0.67–0.93)
ABIRATERONE				
COU-AA-302 2013, 2014, 2015 [135–137]	abiraterone + prednisone	placebo + prednisone	No previous docetaxel ECOG 0–1 PSA or radiographic progression No or mild symptoms No visceral metastases	**OS: 34.7 vs. 30.3 mo.** (HR: 0.81, p = 0.0033) **FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.** (p < 0.0001)
ENZALUTAMIDE				
PREVAIL 2014 [138]	enzalutamide	placebo	No previous docetaxel ECOG 0–1 PSA or radiographic progression No or mild symptoms 10% had visceral mets	**OS: 32.4 vs. 30.2 mo.** (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60–0.84) **rPFS: 20.0 mo. vs. 5.4 mo.** HR: 0.186 (95% CI: 0.15–0.23) p < 0.0001)
SIPULEUCEL-T				
IMPACT 2010 [139]	sipuleucel-T	placebo	Some with previous docetaxel ECOG 0–1 Asymptomatic or minimally symptomatic ECOG 0–1 No visceral met. No corticosteroids	**OS: 25.8 vs. 21.7 mo.** (p = 0.03 HR: 0.78, 95% CI: 0.61–0.98). **FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo.** (no difference)
2006 [140]	sipuleucel-T	placebo		**OS: 25.9 vs. 21.4 mo.** (p = 0.1) **FU: 36 mo. PFS: 11.7 vs. 10.0 wk.**
COMBINATIONS				
PROpel [114,115]	olaparib (300 mg BID) + abiraterone (1000 mg/d) + prednisone (5 mg BID)	placebo + abiraterone + prednisone	ECOG 0–1 regardless of HRRm (retrospective testing) prior taxane for mHSPC allowed	**ibPFS in ITT population: 24.8 vs. 16.6 mo.;** HR: 0.66; 95% CI: 0.54–0.81; (p = 0.001) ibPFS in *BRCA*+: HR 0.24; 95% CI: 0.12–0.45 **OS in ITT population: 42.1 vs. 38.9 mo.;** HR 0.81; 0.95% CI: 0.81, 0.67–1.0; (p= 0.054)OS in *BRCA*+: HR 0.30; 95% CI: 0.15–0.59
MAGNITUDE [120,141]	niraparib 200 mg/d + abiraterone (1000 mg/d plus prednisone 5 mg BID)	placebo + abiraterone (1000 mg/d plus prednisone 5 mg BID)	ECOG 0–1 AAP ≤ 4 mo allowed for mCRPC HRR-biomarker-positive cohort prior docetaxel for mHSPC allowed prior ARPI for mHSPC allowed prior ARPI for mCRPC allowed	**rPFS (central review) in HRR+: 16.5 vs. 13.7 mo.** HR = 0.73; 95% CI: 0.56–0.96; (p = 0.022) **rPFS (central review) in *BRCA* 1/ 2+:** rPFS 19.5 versus 10.9 months; HR= 0.55; 95% CI 0.39–0.78; (nominal p= 0.0007)
TALAPRO-2 [109,123–126]	talazoparib (0.5 mg/d) + enzalutamide (160 mg/d)	enzalutamide + placebo	ECOG 0–1 All comers: HHR deficient and HRR non-deficient or unknown prior AAP or docetaxel allowed for mHSPC	**rPFS in ITT: NR (27.5-NR) vs. 21.9 mo.:** HR 0.63; 95% CI: 0.51–0.78 (p<0.0001); rPFS 33.1 vs. 19.5 mo.: HR 0·67; 95% CI 0·55–0·81; (p<0·0001); rPFS in *BRCA*+: HR 0.23; 95% CI: 0.10–0.53 p=0.0002 **Cohort 1:** OS in ITT (HRR- and HRR+): 45.8 vs. 37.0 mo. - HR 0.80; 95% CI: 0.66–0.96 (p=0.016); OS in HRR+: HR 0.55 95% CI 0.36–0.83; (p=0·0035) HRR- or unknown: HR 0.88; 0.71–1.08 (p=0.22) **Cohort 2:** ITT= HRR+ OS 45.1 vs. 31.1 mo.: HR 0.62; 95% CI 0.48–0.81; (two-sided p=0·0005); BRCA1/2+: OS NR vs. 28.5 mo.: HR 0.50; 95% CI 0.32–0.78; (p=0·0017); 4-yr., OS 53% vs 23%
PEACE-3 [130]	enzalutamide 160 mg/d + radium 223 (6 cycles)	enzalutamide	asymptomatic or mildly symptomatic ≥ 2 bone metastases, +/- additional lymph node metastases no visceral metastases prior docetaxel or abiraterone for mHSPC allowed bone protection mandatory (after amendment)	rPFS: 19.4 vs. 16.4 mo.: HR 0.69, 95% CI 0.54-0.87, (p=0.0009), OS: 42.3 vs. 35.0 mo.: HR 0.69, 95% CI 0.52-0.90, (p=0.0031)

BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mets. = metastases; mo. = months; ib = imaging based; (r)PFS = (radiographic) progression-free survival; OS = overall survival; IHC = immunohistochemistry; HRRm = homologous recombination repair genes mutation; BRCA+ = BRCA gene mutated; ITT = intention to treat; BICR = blinded independent central review.

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the EMA for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated [57]. In the United States of America (USA), the FDA has approved olaparib with AAP for mCRPC patients with deleterious or suspected deleterious *BRCA* mutations as determined by an FDA-approved companion diagnostic test [117].

The combination of PARP inhibitor plus ARPI in patients with *BRCA* 1/2 (or *ATM*) mutations in the first-line, as opposed to the use of PARP inhibitor monotherapy or the sequential use of these agents, is supported by a randomised phase II trial (BRCAAway), albeit with low patient numbers and thus a low level of evidence [118].

5.2.2.2. Abiraterone/prednisone plus niraparib. In a randomised, double-blind, phase III trial (MAGNITUDE), AAP plus niraparib 200 mg once daily or placebo, was evaluated [119]. The study prospectively included two cohorts, an *HRR*-negative and an *HRR*-positive cohort. The *HRR*-negative cohort was closed early for futility after enrolling 200 patients. In the overall *HRR*-positive cohort, the addition of Niraparib to AAP resulted in a significant improvement in the first endpoint rPFS compared to AAP plus placebo (HR: 0.73; 95% CI: 0.56–0.96; p = 0.0217) and the median rPFS was 16.5 versus 13.7 months in favour of the combination. In particular, the 113 patients with *BRCA* 1/2 mutations who received AAP plus niraparib [120] derived a major rPFS benefit (19.5 vs. 10.9 months; HR:0.55; 95% CI: 0.39–0.78; nominal p = 0.0007). The final analysis of OS at median follow-up of 37.3 months revealed no difference between niraparib + AAP and placebo + AAP in the *HRR*-positive population (HR: 0.931; 95% CI: 0.72-1.20; p = 0.585) or the subgroup with *BRCA* 1/2 alterations (HR: 0.788; 95% CI: 0.55-1.120; nominal p = 0.183) [121]. The most common side effects with Niraparib plus AAP in the ITT population were anaemia (46.2%), fatigue (26.4%), hypertension (31.6%) and constipation (30.7%). The combination of niraparib plus AAP in a dual-action tablet has been approved by the EMA and the FDA for patients with mCRPC and *BRCA* 1/2 mutations in whom chemotherapy is not clinically indicated [122].

5.2.2.3. Enzalutamide plus Talazoparib. A randomised double-blind, phase III trial (TALAPRO-2) of the PARP inhibitor talazoparib (0.5 mg daily) plus enzalutamide versus enzalutamide/placebo showed a significantly better median rPFS (first endpoint) in favour of the combination regardless of the *HRR* pathway status [123]. The median rPFS was 33.1 months (95% CI: 27.4–39.0) versus 19.5 months (16.6–24.7); (HR: 0.67; 95% CI: 0.55–0.81; p < 0.0001).

For the subgroups of patients with *HRR* mutations, the benefit of the combination was much more pronounced. The *HRR* gene-mutated population showed a median rPFS of 27.9 (16.6–not reached) for the talazoparib combination versus 16.4 (10.9–24.6) for the placebo group (0.46; 95% CI: 0.30–0.70; p = 0.0003) and 0.70 (0.54–0.89; p = 0.0039) in patients with a status of non-deficient or unknown. In an exploratory analysis, the HR for rPFS in patients with *BRCA*-mutated mCRPC was 0.23 (0.10–0.53; p = 0.0002) and in patients with non-*BRCA*m *HRR* gene-mutated mCRPC, it was 0.66 (0.39–1.12; p = 0.12) in favour of the talazoparib combination [123]. At a median follow-up of 52.5 months, OS was significantly improved with talazoparib plus enzalutamide compared with enzalutamide plus placebo (HR: 0.80; 95% CI: 0.66–0.96; p = 0.016); median OS was 45.8 months in the talazoparib group compared with 37.0 months in the control group. This effect was much more pronounced in *HRR*-deficient patients (n = 69; HR: 0.55; 95% CI: 0.36–0.83; p = 0.0035) and to a much lesser extent in *HRR*-non-deficient or unknown patients (n = 636; HR: 0.88; 95% CI: 0.71–1.08; p = 0.22). At the final updated analysis, rPFS showed a slightly higher HR (HR: 0.67; 95% CI: 0.55–0.81; p < 0.0001) [124].

The most common treatment-emergent AEs with the addition of talazoparib were anaemia, neutropenia, and fatigue [123]. In TALAPRO-2, an *HRR*-deficient-only cohort (cohort 2; n = 230) was recruited. The primary analysis for the combined *HRR*-deficient population (n = 399) met the rPFS endpoint with a HR 0.45 (95% CI: 0.33-0.61; p < 0.0001; median not reached at the time of the analysis for the talazoparib group vs. 13.8 months for the placebo group). At median follow-up of 44.2 months, talazoparib plus enzalutamide resulted in a statistically significant improvement in OS versus enzalutamide (HR: 0.62; 95% CI: 0.48–0.81; two-sided p =0.0005) in this cohort of *HRR* deficient patients. The median OS was 45.1 months (95% CI: 35.4 - not reached) in the talazoparib group versus 31.1 months in the control group. In the subgroup of patients with *BRCA* 1/2 alterations (n = 155 [39%]), median OS was not reached for talazoparib plus enzalutamide versus 28.5 months for enzalutamide (HR: 0.50; 95% CI: 0.32–0.78; p = 0.0017); four-year OS rates were 53% in the talazoparib group versus 23% in the control group. Updated rPFS favoured talazoparib plus enzalutamide versus enzalutamide (HR: 0.47; 95% CI: 0.36–0.61; p < 0.0001; median rPFS was 30.7 vs. 12.3 months) [125,126]. The expected clinical benefit in the subgroups needs to be weighed against the potential burden of side effects [109].

The FDA approved talazoparib with enzalutamide only for *HRR* gene-mutated mCRPC [109,125,127]. In May 2025, the Oncologic Drugs Advisory Committee (ODAC) of the FDA deemed the results from TALAPRO-2 insufficient to conclude a favourable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-*HRR*m mCRPC [128]. The EMA has approved the combination of talazoparib and enzalutamide for the treatment of patients with mCRPC in whom chemotherapy is not clinically indicated [129].

5.2.3. Radium-223 in combination with enzalutamide

Men with mCRPC and bone metastases were randomised 1:1 to enzalutamide with or without radium-223 (ENZ vs. ENZ-RAD) in the EORTC 1333/PEACE-3 trial [130]. After an amendment, co-administration of zoledronic acid or denosumab (bone protecting agents [BPA]) was obligatory. The primary endpoint was rPFS. Of the 446 enrolled men, 87.9% in the ENZ-RAD arm completed the scheduled six cycles of RAD. Radiographic PFS was 16.4 (95% CI: 13.8-19.2) months in the ENZ arm and 19.4 (95% CI: 17.1-25.3) months in the ENZ-RAD arm. The HR for rPFS was 0.69 (95% CI: 0.54-0.87; p = 0.0009). The HR for OS was 0.69 (95% CI: 0.52-0.90; p = 0.0031), with median OS in the pre-

planned interim analysis of 35.0 (95% CI: 28.8-38.9) months in the ENZ arm and 42.3 (95% CI: 36.8-49.1) months in the ENZ-RAD arm. Treatment-emergent AEs ≥ grade 3 were reported in 55.8% and 65.6% of the patients in the ENZ and ENZ-RAD arms, respectively. The most frequent grade ≥ 3 treatment-emergent AEs in the ENZ-RAD arm were hypertension (34%), fatigue (6%), anaemia (5%), and neutropenia (5%). No treatment-emergent AEs ≥ grade 3 was increased by more than 5% in the ENZ-RAD arm versus the ENZ arm.

The interim safety data analysis from the randomised phase III PEACE-3 trial comparing radium-223 combined with enzalutamide for first-line mCPRC to enzalutamide alone showed a high fracture rate in both arms. For patients who received BPA therapy after it became mandatory on the trial, fracture rates significantly decreased in both study arms. One-year fractures decreased from 15.6% to 2.6% with a BPA in patients receiving enzalutamide monotherapy. This underscores the high risk of fracture in patients with mCRPC and the necessity of complying with guidelines regarding BPA administration in the ARPI era [131].

5.3. Second-line treatment for mCRPC

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 8. There is a paucity of high-level data with regards to the sequence of treatments, particularly in case of pretreatment for mHSPC with ARPI and/or docetaxel or other agents. Treatment sequences will depend on which agents were used previously.

5.3.1. ^{177}Lu-PSMA-617 after ARPI

Primary and updated analyses of rPFS for the phase III, multicentre RCT, PSMAfore, investigating taxane-naive patients with PSMA-positive mCRPC who had progressed on ARPI, have been published. Patients were 1:1 randomised between open-label, intravenous ^{177}Lu-PSMA-617 (7.4 GBq intravenously, every six weeks, for up to six cycles) and a change of ARPI. A total of 468 patients met all eligibility criteria and were randomly assigned to receive ^{177}Lu-PSMA-617 (234 [50%] patients) or ARPI change (234 [50%]). Crossover was allowed. In the updated analysis at time of the third data cut-off (median time from randomisation to third data cut-off 24.11 months [IQR 20.24–27.40]), median rPFS was 11.60 months (95% CI: 9.30–14.19) in the ^{177}Lu-PSMA-617 group versus 5.59 months (4.21–5.95) in the ARPI change group (HR 0.49; 95% CI: 0.39–0.61) [142].

In the final analysis, the key secondary endpoint of OS did not show a statistically significant difference between the ^{177}Lu-PSMA-617 and the ARPI arms. In total, 141/234 participants (60.3%) randomised to ARPI change crossed over to receive ^{177}Lu-PSMA-617. The median OS was 24.48 months with ^{177}Lu-PSMA-617 versus 23.13 with ARPI change (HR: 0.91; 95% CI: 0.72–1.14; p = 0.20). For ^{177}Lu-PSMA-617 versus ARPI change, exposure-adjusted incidences of grade ≥ 3 and serious treatment-emergent AEs were 60.8 versus 85.1 and 32.5 versus 49.9 per 100 patient-treatment years, respectively [143]. In the ^{177}Lu-PSMA-617 arm, dry mouth occurred in 135/227 participants (59.5%; 2/227 grade ≥ 3) and anaemia in 62/227 (27.3%; 14/227 grade ≥ 3).

5.3.2. Rucaparib after ARPI

The phase III TRITON-3 trial randomised 405 mCRPC patients [112]. Patients were selected for a *BRCA* 1, *BRCA* 2, or *ATM* alteration and disease progression after treatment with an ARPI for mCRPC. Treatment was as follows: rucaparib 600 mg twice daily or a physician's choice control, either second line docetaxel or the ARPI which had not been given previously. The first endpoint rPFS in the ITT group was significantly better with rucaparib (median 10.2 months and 6.4 months, respectively; HR: 0.61; 95% CI: 0.47-0.80; p < 0.001). The small ATM subgroup did not derive a benefit. An interim analysis revealed OS to be immature. The study design allowed for cross-over and 60% of patients received a PARP inhibitor at progression (47% rucaparib). With regards to the control arms, the median rPFS was longer with rucaparib than with docetaxel (11.2 months vs. 8.3 months; HR: 0.53; 95% CI: 0.37-0.77) and it was also longer than with an ARPI (11.2 months vs. 4.5 months; HR: 0.38; 95% CI: 0.25-0.58). The most frequent AEs with rucaparib were fatigue, nausea, and anaemia, including 24% grade ≥ 3 anaemia and 29% of patients on rucaparib required at least one blood transfusion [144]. Rucaparib has been approved by the FDA.

5.4. Treatment after docetaxel and one line of ARPI for mCRPC

5.4.1. PSMA-based therapy

The PSMA therapeutic radiopharmaceutical supported by the most robust data is ^{177}Lu-PSMA-617. In TheraP, patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by ^{68}Ga-PSMA-11 and ^{18}FDG PET-CT scans, were randomised to receive ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously, every six weeks, for up to six cycles) or cabazitaxel (20 mg/m^2 for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for ^{177}Lu–PSMA-617 vs. cabazitaxel, respectively, by ITT; difference 29% [95% CI: 16–42]; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016) [145]. Overall survival was similar between randomly assigned patients in the two groups (19.1 vs. 19.6 months; difference -0.5; 95% CI: -3.7-2.7; p = 0.77) [146,147].

An open-label phase III trial (VISION) compared ^{177}Lu-PSMA-617 radioligand therapy (RLT) with protocol-permitted SOC (i.e. excluded chemotherapy, immunotherapy, radium-223 and investigational drugs) in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARPI and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. More than 800 patients were randomised. ^{177}Lu-PSMA-617 plus SOC significantly prolonged both ibPFS and OS, as compared with SOC alone. Grade 3 or above AEs were higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. ^{177}Lu–PSMA-617 has shown to be an additional treatment option in this mCRPC population [148]. In a post hoc analysis of the phase III VISION trial, the magnitude of PSA decline was associated with improvement in clinical and patient-reported outcomes in patients with mCRPC

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Table 8 – Phase II/III randomised controlled trials in second-line/third-line mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [158]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel ECOG 0–2 PSA or radiographic progression	**OS: 15.8 vs. 11.2 mo.** ($p < 0.0001$, HR: 0.74; 95% CI: 0.64–0.86; $p < 0.0001$). FU: 20.2 mo. **rPFS: 5.6 vs. 3.6 mo.**
COU-AA-301 2011 [159]				**OS: 14.8 vs. 10.9 mo.** ($p < 0.001$ HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**
Radium-223				
ALSYMPCA 2013 [160]	radium-223	placebo	Previous or no previous docetaxel ECOG 0–2 Two or more symptomatic bone metastases No visceral metastases	**OS: 14.9 vs. 11.3 mo.** ($p = 0.002$, HR: 0.61; 95% CI: 0.46–0.81). All secondary endpoints show a benefit over best SOC.
CABAZITAXEL				
TROPIC 2013 [161]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel ECOG 0–2	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 mo. OS $\geq$ 2 yr. 27% vs. 16% PFS
TROPIC 2010 [162]				**OS: 15.1 vs. 12.7 mo.** ($p < 0.0001$, HR: 0.70; 95% CI: 0.59–0.83). FU: 12.8 mo. **PFS: 2.8 vs. 1.4 mo.** ($p < 0.0001$, HR: 0.74, 95% CI: 0.64–0.86)
CARD 2019 [106]	cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	ARPI: abiraterone + prednisone OR Enzalutamide	Previous docetaxel Progression $\leq$ 12 mo. on prior alternative ARPI (either before or after docetaxel)	**Med OS 13.6 vs. 11.0 mo.** ($p = 0.008$, HR: 0.64, 95% CI: 0.46–0.89). **rPFS 8.0 vs. 3.7 mo.** ($p < 0.001$, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.
ENZALUTAMIDE				
AFFIRM 2012 [163]	enzalutamide	Placebo	Previous docetaxel ECOG 0–2	**OS: 18.4 vs. 13.6 mo.** ($p < 0.001$, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35–0.47, $p < 0.0001$).
PARP inhibitor				
PROfound 2020 [153,154,164]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARPI, alterations in HRR genes	**rPFS: 7.39 vs. 3.55 mo.** ($p < 0.0001$, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). **OS: 19.1 mo vs. 14.7 mo** (in patients with *BRCA1/2*, ATM alterations) ($p = 0.0175$; HR 0.69; 95% CI: 0.5–0.97).
TRITON-3 [112]	rucaparib (600 mg BID)	docetaxel or abiraterone acetate or enzalutamide	EOCG 0−1 Previous one ARPI *BRCA* 1/2 or ATM alteration	**rPFS: ITT 10.2 mo vs. 6.4 mo,** (HR 0.61; 95% CI, 0.47 to 0.80; $p < 0.001$ for both comparisons)
Radioligand therapy				
VISION 2021 [148]	^{177}Lu-PSMA-617 + SOC	SOC alone	Previous at least 1 ARPI and one or two taxane regimens;Mandatory: PSMA-positive gallium-68 (^{68}Ga)–labelled PSMA-PET scan	**Imaging-based PFS: 8.7 vs. 3.4 mo.** ($p < 0.001$; HR 0.40; 99.2% CI: 0.29–0.57) OS: **15.3 vs. 11.3 mo.** ($p < 0.001$; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [145,146]	^{177}Lu-PSMA-617 (8.5 GBq i.v.q. 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	^{177}Lu-PSMA-617 1:1 randomisation cabazitaxel (20 mg/m^2 i.v.q. 3-weekly, up to 10 cycles)	Post docetaxel Suitable for cabazitaxel	**First endpoint PSA reduction of > 50%:** 66 vs. 37 PSA responses; 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; $p < 0.0001$; and 66% vs. 44% by treatment received; difference 23% [9–37]; $p = 0.0016$). **Secondary endpoint OS:** 19.1 vs. 19.6 mo (^{177}Lu-PSMA vs. cabazitaxel). HR: 0.97, 95% CI: 0.7−1.4 ($p = 0.99$)
PSMAfore 2023 [142,143]	177Lu-PSMA-617 at a dosage of 7·4 GBq (200 mCi) ± 10%; 6 cycles	177Lu-PSMA-617 1:1 randomisation to ARPI change (abiraterone or enzalutamide)	One previous ARPI for mCRPCNo previous taxane in CRPC or mHSPC	**First endpoint:** rPFS 3rd data cut-off : 11·60 mo (95% CI 9·30–14·19) vs 5·59 mo (4·21–5·95) (HR 0·49 [95% CI 0·39–0·61]) **OS:** 24.48 vs. 23.13 HR 0.91; 95% CI 0.72–1.14 ($p = 0.20$)

*Only studies reporting survival outcomes as primary endpoints have been included.
ARPI = androgen receptor pathway inhibitor; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; HR = hazard ratio; HRR = homologous recombination repair; Lu = lutetium; mo. = months; OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr. = years.

Table 9 – Recommendations for systemic treatments of castrate-resistant disease Summary statement for mCRPC first line combination therapy: The combination of ARPI plus PARP inhibitors showed a significant rPFS benefit in RCTs for unselected patients. The OS benefit seen with enzalutamide plus talazoparib in the ITT population seems to be driven by the *HRR*-mutated group. The side effects of PARP inhibitors add substantial toxicity to ARPI monotherapy. Therefore, only a weak recommendation is given for the enzalutamide/talazoparib combination in patients without *HRR* or *BRCA 1/2* mutations.

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, ^{177}lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T and, for patients with DNA homologous recombination repair [*HRR*] alterations, olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, and talazoparib/enzalutamide).	Strong
Avoid sequencing of androgen receptor-targeted agents.	Weak
Offer chemotherapy to patients previously treated with an androgen receptor pathway inhibitor (ARPI).	Strong
Offer patients with metastatic castrate-resistant PCa (mCRPC) who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m^2 every three weeks.	Strong
Offer patients previously untreated for mCRPC and harbouring an *HRR* or *BRCA* mutation abiraterone in combination with olaparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer patients previously untreated for mCRPC and harbouring a *BRCA* mutation abiraterone in combination with niraparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer patients previously untreated for mCRPC and harbouring an *HRR* mutation enzalutamide in combination with talazoparib, if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer genetically tested patients without known *HRR* mutations and previously untreated for mCRPC enzalutamide in combination with talazoparib, if the patient is fit for both agents, willing to bear additional side effects, and did not previously receive an ARPI.	Weak
Offer poly(ADP-ribose) polymerase (PARP) inhibitor monotherapy to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA *HRR* alterations.	Strong
Base further treatment decisions regarding mCRPC on PS, previous treatments, symptoms, comorbidities, genomic profile, extent of disease, and patient preference.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel who have progressed within 12 months of treatment with abiraterone or enzalutamide for mCRPC.	Strong
Offer enzalutamide plus radium-223 to asymptomatic or mildly symptomatic mCRPC patients with bone metastases without visceral metastases.	Strong
Offer 177Lu-PSMA-617 to ARPI and docetaxel pre-treated mCRPC patients with one or more metastatic lesions, highly expressing prostate-specific membrane antigen (PSMA) on diagnostic radiolabelled PSMA positron emission tomography/computed tomography (PET/CT) scan and lacking any relevant non-PSMA avid metastases.	Strong
Offer 177Lu-PSMA-617 to ARPI pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on diagnostic radiolabelled PSMA PET/CT scan, if not fit for docetaxel.	Weak

receiving ^{177}Lu-PSMA-617 plus standard of care in VISION [149].

The earlier use of ^{177}Lu-PSMA-617 was studied in patients progressing on the first ARPI for mCRPC (PSMAfore) [142], see Section 5.3.1.

The reintroduction of ^{177}Lu-PSMA therapy has been proposed in relapsed mCRPC patients who initially responded to PSMA-radionuclide therapy experiencing partial remission but relapsed into progression after a certain period of remission. Several authors have investigated the feasibility of this approach in terms of safety and efficacy. In a retrospective analysis, 47 patients with mCRPC who had biochemical response to initial ^{177}Lu-PSMA-617 RLT followed by disease progression received at least one (up to three) series of ^{177}Lu-PSMA-617 RLT rechallenge. After one series of RLT rechallenge, a PSA decline of at least 50% was achieved in 57%. The median PFS of all patients was 8.7 months and the median OS was 22.7 months [150].

There is an increasing interest in PSMA-targeted alpha therapy (^{225}Ac-PSMA) due to the ability to deliver potent higher local radiation more selectively to cancer cells than PSMA-targeted beta therapy, while minimising unwanted damage to the surrounding normal tissues. A meta-analysis, including nine studies with 263 patients, investigated the therapeutic effects of ^{225}Ac-PSMA RLT in patients with mCRPC, pretreated with chemotherapy, ^{177}Lu-PSMA and/or radium-223. The pooled proportions of patients with more than 50% PSA decline and any PSA decline were 60.99% (95% CI: 54.92–66.83%) and 83.57% (95% CI: 78.62–87.77%), respectively. The estimated mean PFS and mean OS were 9.15 months (95% CI: 6.69–11.03 months) and 11.77 months (95% CI: 9.51–13.49 months), respectively. These findings suggest that ^{225}Ac-PSMA RLT may be an effective treatment option for patients with mCRPC [151]. Despite the encouraging therapeutic response and survival of patients who received ^{225}Ac-PSMA RLT, major AEs such as xerostomia and severe haematotoxicity must be considered as possible reasons for dose reduction or discontinuation of the therapy.

So far, ^{225}Ac-PSMA RLT for mCRPC has not been approved.

Combined therapies, including 177Lu-PSMA radionuclide therapy, in mCRPC have moved into the focus of clinical research. In an open-label, multicentre, randomised, phase II trial, EnzaP, participants not previously treated with docetaxel or an ARPI for mCRPC were randomly assigned (1:1) to enzalutamide 160 mg daily alone or adaptive-dosed (two or four doses) 7.5 GBq ^{177}Lu-PSMA-617 intravenous, every six to eight weeks, based on a 12-week interim PSMA PET/CT [152]. The primary endpoint was PSA PFS. Overall, 83 men were assigned to the enzalutamide plus ^{177}Lu-PSMA-RLT group, and 79 were assigned to enzalutamide alone. Median PSA PFS was 13.0 months (95% CI: 11.0–17.0) in the enzalutamide plus RLT group and 7.8 months (95% CI:

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4.3–11.0) in the enzalutamide group (HR 0.43, 95% CI: 0.29–0.63, p < 0.0001). The most common AEs were fatigue (75%), nausea (47%), and dry mouth (40%) in the enzalutamide plus RLT and fatigue (70%), nausea (27%], and constipation (23%) in the enzalutamide alone group [152]. The actual benefit of the combined use, in particular, in patients pretreated by one or two ARPIs is still to be proven in larger prospective controlled trials, and a firm recommendation would be premature.

5.4.2. *PARP inhibitor monotherapy for mCRPC*

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARPI in mCRPC with alterations in ≥ one of any qualifying gene with a role in *HRR* and progression on an ARPI. Most patients were heavily pretreated with one to two chemotherapies and up to two ARPIs [153,154]. Radiographic PFS by blinded independent central review in the *BRCA* 1/2 or *ATM* mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49; 95% CI: 0.38–0.63). The final results for OS demonstrated a significant improvement among men with *BRCA* 1/2 or *ATM* mutations (Cohort A) (p = 0.0175; HR: 0.69; 95% CI: 0.50– 0.97). This was not significant in men with any (other) *HRR* alteration (Cohort B) (HR: 0.96; 95% CI: 0.63–1.49).

The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib versus enzalutamide/abiraterone. Among patients receiving olaparib, 16.4% discontinued treatment secondary to an AEs, compared to 8.5% of patients receiving enzalutamide/abiraterone. Of patients receiving olaparib, 4.3% had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This was the first trial to show a benefit for genetic testing and precision medicine in mCRPC.

The FDA approved olaparib for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with BRCA1 and BRCA2 alterations [155]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib has been approved by the FDA for patients with deleterious *BRCA* mutations (germline and/or somatic) who have been treated with ARPI and a taxane-based chemotherapy [156]. Approval was based on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious *BRCA* mutations was 43.5% (95% CI: 31–57) [157]. Rucaparib second line after ARPI was studied in the TRITON 3 trial and is discussed in Section 5.3.2.

6. Conclusions

The present text represents a summary of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines for treatment of relapsing, metastatic, and castration-resistant PCa. For more detailed information and a full list of references, refer to the full-text version. These Guidelines are available on the EAU website (http://uroweb.org/guideline/prostate-cancer/).

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