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Editor's choice

EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Part II—2024 Update: Treatment of Relapsing and Metastatic Prostate Cancer

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Abstract

Background and objective: The European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Urological Pathology (ISUP)-International Society of Geriatric Oncology (SIOG) guidelines on the treatment of relapsing, metastatic, and castration-resistant

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prostate cancer (PCa) have been updated. Here we provide a summary of the 2024 guidelines.

Methods: The panel performed a literature review of new data, covering the time frame between 2020 and 2023. The guidelines were updated and a strength rating for each recommendation was added on the basis of a systematic review of the evidence.

Key findings and limitations: Risk stratification for relapsing PCa after primary therapy may guide salvage therapy decisions. New treatment options, such as androgen receptor–targeted agents (ARTAs), ARTA + chemotherapy combinations, PARP inhibitors and their combinations, and prostate-specific membrane antigen–based therapy have become available for men with metastatic PCa.

Conclusions and clinical implications: Evidence for relapsing, metastatic, and castration-resistant PCa is evolving rapidly. These guidelines reflect the multidisciplinary nature of PCa management. The full version is available online (http://uroweb.org/guideline/prostate-cancer/).

Patient summary: This article summarises the 2024 guidelines for the treatment of relapsing, metastatic, and castration-resistant prostate cancer. These guidelines are based on evidence and guide doctors in discussing treatment decisions with their patients. The guidelines are updated every year.

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1. Introduction

A prior summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2020 [1]. This paper summarises the 2024 version of the guidelines on the treatment of relapsing, metastatic, and castration-resistant PCa (CRPC). 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 was assigned for each recommendation.

2. Methods

For the 2024 update of the EAU-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and 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 via 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 (www.uroweb.org/guidelines). Recommendations in the guidelines were developed by the panel to prioritise clinically important care decisions. The strength of each recommendation was determined according to 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. Recommendations are strong when the evidence quality is high and/or there is a favourable balance of benefits to harms and patient preferences. Recommendations are weak when the evidence is of lower quality and/or the benefits and patient preferences are less clear [3].

3. Guidelines

3.1. Diagnosis and treatment of relapse after curative therapies

3.1.1. Definitions

After radical prostatectomy (RP), the threshold that best predicts further metastases is a prostate-specific antigen (PSA) level >0.4 ng/ml that is rising [4–6]. However, with access to ultrasensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients. The RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure after primary radiotherapy (RT) is "any PSA increase >2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir" [7]. After high-intensity focused ultrasound (HIFU) or cryotherapy, no PSA endpoints have been validated against clinical progression or survival [8].

A systematic review and meta-analysis investigated the impact of biochemical recurrence (BCR) on clinical endpoints and concluded that patients experiencing BCR are at higher risk of developing distant metastases and PCa-specific and overall mortality [8]. However, the effect size of BCR as a risk factor for developing clinical evidence of metastatic spread or mortality is highly variable.

Table 1 – European Association of Urology risk categories for patients developing biochemical recurrence

	EAU Low-risk biochemical recurrence	EAU High-risk biochemical recurrence
After RP	PSA doubling time >1 yr and Pathological ISUP grade group <4	PSA doubling time ≤1 yr or Pathological ISUP grade group 4–5
After RT	Interval to biochemical failure > 18 mo and Biopsy ISUP grade group <4	Interval to biochemical failure ≤18 mo or Biopsy ISUP grade group 4–5

ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

On the basis of this meta-analysis, there is a proposal is to stratify patients into two risk categories, since not all patients with BCR will have similar outcomes (Table 1). The prognostic value of stratification as EAU "low-risk" or "high-risk" BCR after RP has been validated in a European cohort [9].

3.1.2. *The role of imaging in PSA-only recurrence*

After RP, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is the imaging modality with the highest sensitivity at low PSA levels and may help in 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 RT (SRT) [10–12]. Magnetic resonance imaging (MRI) after RT has shown excellent results in detecting local recurrences and guiding prostate biopsy [13–15]. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences who are fit for these salvage therapies. Guidelines for imaging in patients with BCR are summarised in Table 2.

3.1.3. *Treatment of PSA-only recurrences after RP*

Early SRT provides the possibility of cure for patients with increasing PSA after RP. The RADICALS, RAVES, and GETUG-AFU 17 trials reported 5-yr biochemical progression–free survival rates of 88%, 87%, and 90%, respectively, for post-RP patients in the SRT group [16–18]. In a matched-pair analysis of 1832 patients with BCR (603 received SRT without androgen deprivation therapy [ADT], 1229 had an observational strategy), metastasis-free survival (MFS) and overall survival (OS) rates at 15 yr after RP were 84.3% versus 76.9%, and 85.3% versus 74.4% for SRT versus no SRT, respectively [19]. The PSA level at BCR was prognostic [20]. In a retrospective multicentre study that included 25 551 patients with at most one high-risk factor after RP (ISUP grade group 4–5 or pT3/4), SRT initiation at a PSA level >0.25 ng/ml was associated with greater risk of all-cause mortality (adjusted hazard ratio [HR] 1.49, 95% confidence interval [CI] 1.11–2.00; p = 0.008) in comparison to SRT initiation when PSA was ≤0.25 mg/ml [21].

Table 2 – Summary of evidence and guidelines for imaging in patients with biochemical recurrence

Recommendation	Strength rating
PSA recurrence after radical prostatectomy	
Perform PSMA PET/CT if the PSA level is >0.2 ng/ml and if the results will influence subsequent treatment decisions (EAU BCR risk groups).	Weak
If PSMA PET/CT is not available and the PSA level is ≥1 ng/ml, perform fluciclovine or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine or choline PET/CT in patients fit for curative salvage treatment.	Strong

BCR = biochemical recurrence; CT = computed tomography; EAU = European Association of Urology; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; PSA = prostate-specific antigen.

The EAU BCR risk definitions may be helpful for individualised treatment decisions. Despite the indication for SRT, a "wait and see" strategy remains an option for the EAU BCR low-risk group [22].

Randomised controlled trials (RCTs) comparing SRT combined with ADT versus SRT alone [23–25] are summarised in Table 3.

A systematic review addressing the benefit from combining hormone therapy with SRT suggested risk stratification of patients on the basis of pre-SRT PSA (<0.5 vs 0.6–1 vs >1 ng/ml), surgical margin status, and ISUP grade as a framework to individualise treatment [26].

A prospective multicentre study enrolled 260 men with rising PSA after RP between 2015 and 2017. PSMA PET results were negative in 34.6% cases and revealed disease confined to the prostatic fossa in 21.5%, disease in the pelvic lymph nodes (LNs) in 26.2%, and distant disease in 17.7%. PSMA PET results were highly predictive of progression-free survival (PFS) at 3 yr for men undergoing SRT for BCR after RP. In particular, men with negative PSMA PET results or disease identified as still confined to the prostatic fossa experienced high freedom from progression, despite receiving less extensive RT and lower rates of additional ADT than those with disease outside the fossa [27]. PSMA PET/CT might be able to stratify men into groups with high versus poor responses to SRT. Imaging at recurrence should only be performed if the result will affect treatment planning. Negative PET/CT findings should not delay SRT if it is otherwise indicated. Guidelines for second-line therapy after treatment with curative intent are summarised in Table 4.

Three prospective RCTs have compared adjuvant RT (ART) and early SRT (RADICALS [16], RAVES [17], and GETUG-AFU 17 [18]). In addition, a preplanned meta-analysis of all three trials has been published (Table 5) [28]. RADICALS-RT included 1396 patients with the option of subsequent inclusion in RADICALS-HT. The primary endpoint was biochemical PFS for RAVES and GETUG-AFU 17, and MFS for RADICALS-RT. With median follow-up between 4.9 yr and 6.25 yr, there was no statistically significant difference in biochemical PFS between the treatments in these trials (Table 5). There was a significantly lower rate of grade ≥2 genitourinary late side effects and grade 3–4 urethral strictures in favour of early SRT. The proportion of patients with adverse pathology at RP (ISUP grade group 4–5 and pT3 with or without positive margins) in the three trials was low (10–20%) and therefore even the meta-analysis may have been underpowered to show an outcome difference [28]. In addition, the side-effect profile may have been impacted, with a larger proportion of ART patients receiving treatment with older three-dimension treatment planning techniques in comparison to SRT patients, and patients treated more recently were more likely to undergo intensity-modulated RT, which has a proven lower rate of late side effects [29]. ART remains a recommended treatment option for highly selected patients with adverse pathology. This recommendation was supported by a retrospective multicentre study comparing ART versus SRT for patients with high-risk features after RP [30]: among men with adverse

Table 3 – Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy versus salvage radiotherapy alone

Study	Patients	Risk groups	mFU (mo)	Regimen	Outcomes
GETUG-AFU 16 2019 [23]	RT + ADT: 369 RT: 374	GG ≤2/3 89% GG ≥4 11% cN0	112	66 Gy PBRT+ 6 mo LHRH-A vs 66 Gy pbRT	10-yr PFS: 64% vs 49% (p < 0.0001) 10-yr MFS: 75% vs 69% (p = 0.034)
RTOG 9601 2017 [24]	RT + ADT: 384 RT: 376	pT2 R1, pT3 cN0	156	64.8 Gy pbRT + 24-mo bicalutamide vs 64.8 Gy pbRT + placebo	12-yr cDM: 14% vs 23% (p = 0.005) 12-yr OS: 76% vs 71% (p = 0.04) 12-yr DSM: 5.8% vs 13.4% (p < 0.001)
NRG Oncology/ RTOG 0534 SPPORT [25]	pbRT alone: 564 pbRT + ADT: 578 pbRT +plnRT + ADT: 574	pT2 or pT3 GG <5 Pre-RT PSA 0.1–2.0 ng/ml	8.2 yr [a]	64.8–70.2 Gy pbRT 64.8–70.2 Gy pbRT + 6-mo LHRH-A 64.8–70.2 Gy pbRT + 45 Gy plnRT + 6-mo LHRH-A	5-yr PFS: Group 1: 70.9% Group 2: 81.3% Group 3: 87.4% Group 3 vs 1: p < 0.0001 Group 2 vs 1: p < 0.0001 Group 3 vs 2: p < 0.0027

ADT = androgen deprivation therapy; cDM = cumulative distant metastasis; DSM = disease-specific mortality; PFS = progression free survival; FFP = Freedom From Progression; GG = International Society of Urological Pathology grade group; LHRH = luteinising hormone–releasing hormone analogue; MFS = metastasis-free survival; mFU = median follow-up; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = radiotherapy; yr = year, pbRT = prostate bed RT; plnRT = pelvic lymph node RT.
[a] For survivors.

Table 4 – Guidelines for second-line therapy after treatment with curative intent

Recommendation	Strength rating
BCR after RP	
Offer early salvage intensity-modulated RT/volumetric arc RT plus image-guided RT to men with two consecutive PSA rises.	Strong
A negative PET/CT scan should not delay SRT if otherwise indicated.	Strong
Offer monitoring, including PSA measurement, to patients with EAU low-risk BCR.	Weak
Do not wait for a PSA threshold before starting treatment. Once the decision for 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
BCR after RT	
Offer monitoring, including PSA measurement, to patients with EAU low-risk BCR.	Weak
Only offer salvage RP, brachytherapy, stereotactic body RT, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study conducted in experienced centres.	Strong
Recommendations for systemic salvage treatment	
Do not offer ADT to patients with M0 disease and a PSA doubling time >12 mo.	Strong
Offer enzalutamide with or without ADT to patients with M0 disease with high-risk BCR, defined as a PSA doubling time of ≤9 mo and PSA ≥2 ng/ml above the nadir after RT or ≥1 ng/ml after RP with or without postoperative RT.	Strong
Recommendations for follow-up after RP or RT	
Routinely monitor 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

ADT = androgen deprivation therapy; BCR = biochemical recurrence; CT = computed tomography; EAU = European Association of Urology; PET = positron emission tomography; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SRT = salvage RT.

pathology, ART was associated with a significant reduction in all-cause mortality risk in comparison to early SRT.

3.1.4. *Treatment of PSA-only recurrences after RT*

Therapeutic options in these patients are ADT and salvage local procedures, as well as a "wait and see" approach, depending on performance status, life expectancy, and EAU BCR risk category at relapse. A systematic review and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage 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 RT [31]. There were no significant differences in recurrence-free survival (RFS) between these modalities. The 5-yr RFS rate ranged from 50% after cryotherapy to 60% after HDR BT and SBRT. The authors reported that severe genitourinary toxicity exceeded 21% for HIFU and RP, whereas it ranged from 4.2% to 8.1% for re-irradiation. Differences in severe gastrointestinal toxicity also appeared to favour re-irradiation, particularly HDR BT [31]. Owing to the methodological limitations of the studies (the majority of studies included were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes), the evidence available for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made.

3.1.5. *Hormone therapy for relapse*

A three-arm randomised phase 3 trial (EMBARK) enrolled patients with PCa who had high-risk BCR, defined as a PSA doubling time of ≤9 mo and a PSA level of ≥2 ng/ml above

Table 5 – Overview of three randomised trials and one meta-analysis of adjuvant versus early salvage RT after RP

Study	Pts	Inclusion criteria	Randomisation	BCR definition: PSA (ng/ml)	mFU (yr)	bPFS rate at 5 yr	OS or MFS	Side effects
RAVES TROG 08.03/ ANZUP 2020 [17]	333 [a]	pT3a/pT3b Any T with PSM PSA <0.1 ng/ml after RP	64 Gy ART: PSA <0.1 ng/ml 64 Gy early SRT: PSA >0.2 ng/ml Median pre-SRT PSA NR	>0.4 after RT	6.1	86% vs 87% $p > 0.05$	NR	Late grade ≥2 GUT: 70% vs 54% ($p = 0.002$)
RADICALS-RT 2020 [16]	1396	pT3a/pT3b/pT4 Pre-RP PSA >10 ng/ml Any T + PSM Gleason 7–10 PSA <0.2 ng/ml after RP	ART vs early SRT at PSA >0.1 ng/ml 52.5 Gy (20 Fx) or 66 Gy (33 Fx) Median pre-SRT PSA: 0.2 ng/ml	>0.4 or 2 at any time	4.9	85% vs 88% $p = 0.56$	NR	Self-reported UI at 1 yr: 4.8% vs 4% ($p = 0.023$) UST grade 3/4 at 2 yr: 6% vs 4% ($p = 0.02$)
GETUG-AFU 17 2020 [18]	424 [b]	pT3a/pT3b/pT4a and PSM PSA <0.1 ng/ml after RP	66 Gy ART vs 66 Gy early SRT at PSA 0.1 ng/ml 6-mo LHRH-A in both groups Median pre-SRT PSA 0.24 ng/ml	>0.4	6.25	92% vs 90% $p = 0.42$	NR	Late grade ≥2 GUT: 27% vs 7% ($p < 0.001$) ED: 28% vs 8% ($p < 0.001$)
ARTISTIC meta-analysis 2020 [28]	2153	See above	See above	See above	4.5	89% vs 88% $p = 0.7$	NR	NR

ART = adjuvant RT; BCR = biochemical recurrence; bPFS = biochemical progression-free survival; ED = erectile dysfunction; mFU = median follow-up; Fx = fraction; GUT = genitourinary toxicity; LHRH = luteinising hormone–releasing hormone; med = median; MFS = metastasis-free survival; NR = not reported; OS = overall survival; PSA = prostate-specific antigen; PSM = positive surgical margin; Pts = patients; RP = radical prostatectomy; RT = radiotherapy; SRT = salvage RT; UI = urinary incontinence; UST = urethral stricture.
[a] The target was 470 but the study closed early.
[b] The target was 718, but the study closed early.

the nadir after RT, or ≥1 ng/ml after RP with or without postoperative RT [32]. Patients (M0 on conventional imaging; PSMA PET imaging was not applied for eligibility) were randomly assigned 1:1:1 to receive enzalutamide daily plus leuprolide every 12 wk (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group). Treatment was suspended at week 37 if PSA was <0.2 ng/ml and was restarted when PSA was at least 5.0 ng/ml if the patient had not undergone RP, or at least 2.0 ng/ml if the patient had undergone RP. The primary endpoint was MFS in the combination group in comparison to the leuprolide-alone group. MFS in the monotherapy group in comparison to the leuprolide-alone group was a key secondary endpoint. A total of 1068 patients were randomised. At median follow-up of 60.7 mo, the 5-yr MFS rate 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 regard to MFS (HR 0.42, 95% CI 0.30–0.61; $p < 0.001$). Enzalutamide monotherapy also showed superior MFS to leuprolide alone (HR 0.63, 95% CI 0.46–0.87; $p = 0.005$). The patient-reported outcomes from EMBARK showed that both enzalutamide combination and monotherapy versus leuprolide alone preserved high health-related quality of life in patients with high-risk BCR of prostate cancer [33]. These results led to US Food and Drug Administration (FDA) approval of enzalutamide alone or in combination with ADT for patients with nonmetastatic hormone-sensitive PCa (HSPC) with BCR at high risk of metastasis (high-risk BCR) in November 2023 [34].

3.1.6. *Management of pelvic nodal relapse alone*

Surgical management of recurrent nodal metastases in the pelvis was evaluated in a systematic review [35]. The 5-yr BCR-free survival rate after salvage LN dissection (sLND) ranged from 6% to 31%. The 5-yr OS rate was approximately 84%. In a multicentre retrospective study, long-term outcomes for 189 patients who underwent sLND were worse than previously described in studies with shorter follow-up [36]. The BCR-free survival rate at 10 yr was 11%. The majority of patients had undergone choline PET, and median PSA at sLND was 2.5 ng/ml. In a cohort study that included patients treated with sLND via PSMA-radioguided surgery (RGS), the 2-yr BCR-free survival rate was 32% [37]. Higher preoperative PSA, a higher number of PSMA-avid lesions, and retroperitoneal localisation of lesions on preoperative imaging were independent predictors of BCR after PSMA-RGS. High-level evidence for the oncological value of sLND is still lacking.

OLIGOPELVIS GETUG P07, a multicentre phase 2 trial, assessed the efficacy of high-dose salvage elective node RT (ENRT) and ADT (6 mo) in oligorecurrent (≤5 lesions) pelvic LN relapses after RP, detected via fluorocholine PET/CT imaging [38]. Image-guided intensity-modulated RT was used to deliver 54 Gy in 1.8-Gy fractions to the whole pelvis, with a simultaneous integrated boost of 66 Gy in 2.2-Gy fractions to pathological pelvic LNs. Patients who had not received previous irradiation received 66 Gy in 2-Gy fractions to the prostatic bed, with up to 72 Gy in 2-Gy fractions in cases of local relapse in the prostatic bed. Between 2014 and July 2016, 67 patients were recruited in 15 centres. Half of the patients had received prior prostatic irradiation. At median follow-up of 49.4 mo, the 2-yr and 3-yr PFS rates were 81% and 58%, respectively. Median PFS was 45.3 mo. The 2-yr and 3-yr BCR-free survival rates were 58% and 46%, respectively.

A retrospective study compared SBRT to ENRT in nodal oligorecurrent PCa (n = 506 patients, 365 with N1 pelvic recurrence) [39]. SBRT was defined as a minimum of 5 Gy

per fraction to each lesion for a maximum of ten fractions. ENRT was defined as a minimum dose of 45 Gy in up to 25 fractions to the elective nodes, with or without a simultaneous boost to the suspicious node(s). Nodal recurrences were detected via PET/CT (97%) or conventional imaging (3%). At median follow-up of 36 mo, ENRT (n = 197) versus SBRT (n = 309) was associated with a significant reduction in nodal recurrences (2% vs 18%; p < 0.001). Multivariable analysis revealed that patients with one LN at recurrence had longer adjusted MFS after ENRT (HR 0.50, 95% CI 0.30–0.85; p = 0.009). The tendency to relapse was higher for pelvic LNs than for extrapelvic LNs (p < 0.001). For patients presenting with two or more (extra)pelvic LNs, adjusted MFS was not significantly different (HR 0.92, 95% CI 0.54–1.59; p = 0.8). In these situations, ENRT and SBRT should be used in highly selected patients in prospective cohorts or clinical trials only.

3.2. *Metastatic PCa*

All prospective data available rely on the definition of M1 disease on the basis of a CT scan or MRI and bone scintigraphy. The influence of newer, more accurate imaging modalities on treatments and outcomes has not been assessed in randomised trials yet.

Recommendations for first-line treatment of metastatic HSPC (mHSPC) are summarised in Table 6.

3.2.1. *Prognostic factors*

Median survival for patients with newly diagnosed metastases is approximately 50 mo with ADT alone, but is highly variable, as the M1 population is heterogeneous [40].

"Volume" of disease as a potential predictor was introduced in CHAARTED [41–43], and was subsequently shown in STAMPEDE to be predictive in an adequately powered subgroup analysis of the benefit of addition of prostate RT to ADT in the subgroup of patients with low-volume/low-burden disease [44].

It has also been shown that "metachronous" metastatic disease (after radical local treatment of the primary tumour) versus synchronous (or de novo) metastatic disease generally has better prognosis [45].

On the basis of a large SWOG 9346 cohort, the PSA level after 7 mo of ADT was used to define three prognostic groups [46]. PSA ≤0.2 ng/ml at 7 mo was confirmed as a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study, independent of the addition of docetaxel [47]. Similarly, achievement of PSA ≤0.1 ng/ml after 6 mo was correlated with long-term outcomes in the LATITUDE study [48]. For patients treated with ADT and apalutamide, a deep PSA decline, defined as a ≥90% decrease from baseline or to ≤0.2 ng/ml at a landmark of 3 mo, was associated with longer OS [49].

3.2.2. *First-line hormone treatment*

Primary ADT has been the standard of care (SOC) for more than 50 yr [50]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, or for orchidectomy or for a luteinising hormone–releasing hormone (LHRH) agonist or antagonist. The decrease in testosterone level is much faster with orchiectomy and LHRH antagonists. Therefore, patients with impending spinal-cord compression or other potential impending complications from their cancer should be treated with either bilateral orchidectomy or LHRH antagonists as the preferred options.

There is a suggestion in some studies and in a systematic review and meta-analysis that cardiovascular side effects are less frequent among patients treated with LHRH antagonists than those treated with LHRH agonists [51–54]. Therefore, LHRH antagonists might be considered for patients with pre-existing cardiovascular disease or other cardiovascular risk factors if chemical castration is chosen.

Table 6 – Guidelines for first-line treatment of hormone-sensitive metastatic disease [a]

Recommendation	Strength rating
Offer immediate systemic treatment with ADT to alleviate symptoms and reduce the risk of potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to symptomatic patients with M1 disease.	Strong
Offer short-term administration of an older-generation AR antagonist to patients with M1 disease starting an 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 contraindications for combination therapy and have sufficient life expectancy to benefit from combination therapy (≥1 yr) and are willing to accept the higher risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease who are fit for the regimen.	Strong
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with prostate RT (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 disease according to the CHAARTED criteria.	Strong
Do not offer patients with M1 disease ADT combined with surgery outside of clinical trials.	Strong
Only offer metastasis-directed therapy to patients with M1 disease within a clinical trial setting or a well-designed prospective cohort study.	Strong

ADT = androgen deprivation therapy; AR = androgen receptor; LHRH = luteinising hormone–releasing hormone; RT = radiotherapy.
[a] All the recommendations are for metastatic disease identified via bone scintigraphy and a computed tomography scan or magnetic resonance imaging.

3.2.3. *Combination therapies*

3.2.3.1. ADT combined with chemotherapy. Three large RCTs [41,55,56] compared ADT alone as the SOC to ADT combined with immediate docetaxel. The primary objective in all three studies was to assess OS. Results from CHAARTED and GETUG-AFU15 [41,55] suggested that the volume of metastatic disease modifies the effect of docetaxel, with improved survival observed for patients with high-volume metastases in comparison, but not for patients with low-volume metastases. In STAMPEDE [56], there was no evidence of any heterogeneity of the docetaxel effect between metastatic burden subgroups.

A systematic review and meta-analysis that included these three trials showed that addition of docetaxel to SOC improved survival [57]. The HR of 0.77 (95% CI 0.68–0.87; $p < 0.0001$) translates to an absolute improvement in 4-yr survival of 9% (95% CI 5–14%). A systematic review and meta-analysis of individual-participant data from the three trials showed no meaningful beneficial effect of addition of docetaxel to ADT for patients with metachronous low-volume disease. Interestingly the largest absolute improvement at 5 yr was observed for patients with high-volume disease and clinical stage 4 [58].

On the basis of these data, upfront docetaxel combined with ADT was considered as a standard for men with metastases at first presentation, provided they are fit enough to receive docetaxel [57]. More recently two large phase 3 studies have shown an OS benefit from addition of an androgen receptor pathway inhibitor (ARPI) to ADT and docetaxel (Section 3.2.3.3). Therefore, addition of docetaxel alone to ADT should only be considered if no ARPI is available or all available agents are contraindicated.

3.2.3.2. Combination with an ARPI alone (abiraterone, apalutamide, enzalutamide). Two large RCTs (STAMPEDE and LATITUDE) investigate addition of abiraterone acetate plus prednisone (AAP) to ADT for men with mHSPC [59–61]. Both trials showed a significant OS benefit for the combination. In LATITUDE, which only included patients with de novo high-risk metastatic disease, the HR reached 0.62 (95% CI 0.51–0.76) [60]. The HR in STAMPEDE was very similar at 0.63 (95% CI 0.52–0.76) for the total patient population (metastatic and nonmetastatic disease), and 0.61 for the subgroup of patients with metastatic disease [59]. While only high-risk patients were included in LATITUDE, a post hoc analysis of STAMPEDE showed the same benefit regardless of risk or volume category [62].

Three large RCTs (TITAN, ARCHES, and ENZAMET) assessed the addition of second-generation AR antagonists to ADT in men with mHSPC [63–65]. In ARCHES the primary endpoint was radiographic PFS (rPFS). In the primary analysis, rPFS was significantly better with the combination of enzalutamide + ADT (HR 0.39, 95% CI 0.3–0.5). In ENZAMET, the primary endpoint was OS. Addition of enzalutamide to ADT in the first analysis improved OS (HR 0.67, 95% CI 0.52–0.86) in comparison to ADT plus a nonsteroidal antiandrogen [65]. In a planned later analysis with median follow-up of 68 mo, the OS benefit of enzalutamide addition was maintained (HR 0.7, 95% CI 0.58–0.84) [66]. In the TITAN trial of ADT + apalutamide, and rPFS and OS were co-primary endpoints. In the primary analysis, rPFS was significantly improved by addition of apalutamide (HR 0.48, 95% CI 0.39–0.6); OS at 24 mo was also improved (HR 0.67, 95% CI 0.51–0.89). In the final analysis, the HR for OS was 0.65 (95% CI 0.53–0.79) without adjustment for crossover. The more recently published CHART trial tested ADT plus rezvilutamide versus ADT plus bicalutamide in patients with high-volume de novo metastatic disease. OS and rPFS were co-primary endpoints. At the preplanned interim analysis, rezvilutamide significantly improved rPFS (HR 0.44, 95% CI 0.33–0.58) and OS (HR 0.58, 95% CI 0.44–0.77) in comparison to bicalutamide [67].

3.2.3.3. Combination with docetaxel and an ARPI ("triplet therapy"). Addition of abiraterone to ADT and docetaxel led to rPFS and OS benefits in the PEACE-1 trial [68]. The trial had a 2 × 2 factorial design and participants with de novo (synchronous) metastatic PCa were randomised to SOC (at the beginning of the trial ADT, later ADT + docetaxel for 6 cycles for chemotherapy-fit patients) versus SOC + RT versus SOC + abiraterone versus SOC + RT + abiraterone. The co-primary endpoints were rPFS and OS, and both were statistically significantly improved in the total population. In the group of patients who received ADT + docetaxel as SOC (n = 710) both rPFS (HR 0.50, 95% CI 0.34–0.71) and OS (HR 0.75, 95% CI 0.59–0.95) increased. It is noteworthy that approximately 35% of this population had low-volume disease. Toxicity was modestly increased, and mostly involved hypertension.

In the ARASENS phase 3 trial, all patients (n = 1306) received ADT and docetaxel for six cycles as SOC plus darolutamide or placebo [69]. All patients had metastatic disease, and which 14% had relapsed disease after radical local treatment (metachronous). The primary endpoint of OS and was statistically significantly increased by addition of darolutamide (HR 0.68, 95% CI (0.57–0.8). Interestingly, the incidence of adverse events in the trial was similar in both arms. In both trials, docetaxel and the ARPI were administered concomitantly. Of the patients included, 77% had high-volume and 70% had high-risk disease. In an unplanned subgroup analysis, a beneficial effect of darolutamide addition versus placebo for OS was observed for patients with high-volume disease (HR 0.69, 95% CI 0.57–0.82), patients with high-risk disease (HR 0.71, 95% CI 0.58–0.86), and patients with low-risk disease (HR 0.62, 95% CI 0.42–0.9). In the smaller subgroup of patients with low-volume disease, the results were also suggestive of a survival benefit (HR 0.68, 95% CI 0.41–1.13) [70].

ENZAMET, TITAN, and ARCHES also included patients who received docetaxel as part of the SOC, and thus not all concomitantly, but the percentage of patients receiving docetaxel in these trials was much lower [63–65].

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

The STAMPEDE trial evaluated 2061 men with mHSPC who were randomised to ADT alone versus ADT plus RT to the prostate only. The trial showed that RT to the primary tumour improved OS in the low-volume subgroup (n = 819) [44]. This was confirmed by the latest analysis of long-term follow-up (median 61 mo; HR 0.64 for OS in the low-volume group) [71]. A secondary analysis of the STAMPEDE trial that was not preplanned confirmed the benefit of prostate RT in patients with up to three bone metastases, and also showed a benefit in patients with M1a disease [72]. No evidence of a difference in the time to symptomatic local events was found at median follow-up of >5 yr [71].

Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel and no patients had additional AAP, so no clear recommendation can be made about triple combinations. In addition, it

is not clear if these data can be extrapolated to RP as local treatment, as results from ongoing trials are awaited.

A systematic review and meta-analysis that included two RCTs revealed that, overall, there was no evidence that addition of prostate RT to ADT improved survival for unselected patients (HR 0.92, 95% CI 0.81–1.04; $p = 0.195$) [73]. However, there was a clear difference in the effect of metastatic burden on survival, with an absolute improvement of 7% in 3-yr survival for men who had four or fewer bone metastases.

3.2.5. *Metastasis-directed therapy*

Two randomised phase 2 trials are testing metastasis-directed therapy (MDT) using surgery ± SBRT versus surveillance [74] or SBRT versus surveillance in men with oligorecurrent PCa [75]. Oligorecurrence was defined as fewer than three lesions on choline PET/CT only [74] or conventional imaging with MRI/CT and/or a bone scan [75]. The sample size was small, with 62 and 54 patients, respectively, and a substantial proportion had nodal disease only [74]. ADT-free survival was the primary endpoint in one study, which was longer with MDT than with surveillance [74]. The primary endpoint in the ORIOLE trial was progression after 6 mo, which was significantly lower with SBRT than with surveillance (19% vs 61%; $p = 0.005$) [75]. Combined results from STOMP and ORIOLE confirmed the significant improvement in PFS in favour of MDT (HR 0.44; $p < 0.001$) [76]. A phase 2 trial assessed the biochemical response after ^{18}F-DCFPyL PET/MRI and subsequent MDT. The overall biochemical response rate, defined as a PSA decline≥50%, was 60%, including 22% of patients with a complete biochemical response [77]. There are currently no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as investigational until results from the ongoing RCT are available [78,79].

3.3. *CRPC*

For patients progressing on ADT, it is important to ensure that testosterone levels are confirmed to be <50 ng/dl before diagnosing CRPC. Treatment for CRPC will be influenced by which treatments patients have already been exposed to.

3.3.1. *Nonmetastatic CRPC*

Three large phase 3 RCTs, PROSPER [80], SPARTAN [81], and ARAMIS [82], evaluated MFS as the primary endpoint in patients with nonmetastatic CRPC (M0 CRPC) treated with enzalutamide (PROSPER) placebo, apalutamide (SPARTAN), or darolutamide (ARAMIS) versus placebo. M0 status was established via CT imaging and bone scans. Only patients at high risk of the development of metastasis with a short PSA doubling time of ≤10 mo were included. All trials showed a significant MFS benefit. A survival benefit was shown in the three trials after follow-up of more than 30 mo [83–85].

3.3.2. *Metastatic CRPC*

Patients with metastatic CRPC (mCRPC) should be offered somatic and/or germline molecular testing, as well as testing for mismatch repair deficiencies or microsatellite instability.

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. In general, sequencing of ARPIs such as abiraterone and enzalutamide is not recommended, particularly if the time of response to ADT and to the first ARPI was short (≤6 to 12 mo) and high-risk features of rapid progression are present [86,87].

3.3.2.1. *First-line treatment of mCRPC.*

3.3.2.1.1. Abiraterone. Abiraterone was evaluated in chemotherapy-naïve mCRPC patients in the phase 3 COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [88]. At the final analysis after median follow-up of 49.2 mo, the OS endpoint was significantly positive (34.7 vs 30.3 mo; HR 0.81, 95% CI 0.70–0.93; $p = 0.0033$) [88].

3.3.2.1.2. Enzalutamide. A randomised phase 3 trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [89]. PREVAIL showed a significant improvement in the co-primary endpoints of rPFS (HR 0.186, 95% CI 0.15–0.23; $p < 0.0001$) and OS (HR 0.706, 95% CI 0.6–0.84; $p < 0.001$). A ≥50% decrease in PSA was seen in 78% of patients. Enzalutamide has also been compared with bicalutamide 50 mg/d in a randomised double-blind phase 2 study (TERRAIN) and showed a significant improvement in PFS (15.7 vs 5.8 mo; HR 0.44; $p < 0.0001$) in favour of enzalutamide [90]. Extended follow-up and final analysis confirmed the benefit in OS and rPFS [91].

3.3.2.1.3. Docetaxel. A significant improvement in median survival has been shown with docetaxel-based chemotherapy in comparison to mitoxantrone plus prednisone therapy [92,93].

3.3.2.1.4. Sipuleucel-T. In 2010, a phase 3 trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [94]. Sipuleucel-T is not available in Europe.

3.3.2.1.5. Ipatasertib. The AKT inhibitor ipatasertib in combination with AAP was studied in asymptomatic or mildly symptomatic patients with and without PTEN loss according to immunohistochemistry and previously untreated for mCRPC. The randomised phase 3 trial (IPAtential) showed a significant benefit for the primary endpoint of rPFS in the PTEN loss population (18.5 vs 16.5 mo; HR 0.77, 95% CI 0.61–0.98; $p = 0.0335$) but not in the intention-to-treat (ITT) population. The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhoea [95]. Grade ≥3 adverse events (AEs) occurred nearly twice as often in the combination group, and the discontinuation rate due to AEs was four times higher. This combination is still investigational [96].

3.3.2.1.6. Combinations with PARP inhibitors. On the basis of the suggestion that there is a synergistic antitumour effect when combining an ARPI with a PARP inhibitor, several such combination trials (Table 7) were conducted in first-line mCRPC with different trial designs, different patient selection criteria, and conflicting results.

Table 7 – Randomised phase 3 controlled trials of first-line treatment for mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
Docetaxel				
SWOG 99-16 2004 [108]	DOC 60 mg/m^2 Q3W Estramustine 3 × 280 mg/d	Mitoxantrone 12 mg/m^2 Q3W + P5$_{b.i.d.}$		OS: 17.52 vs 15.6 mo (HR: 0.80, 95% CI 0.67–0.97; p = 0.02) PFS: 6.3 vs 3.2 mo (p < 0.001)
TAX 327 2004, 2008 [92,93]	DOC 75 mg/m^2 Q3W + P5$_{b.i.d.}$ or DOC 30 mg/m^2 weekly + P5$_{b.i.d.}$	Mitoxantrone 12 mg/m^2 Q3W + P5$_{b.i.d.}$		OS: 19.2 vs 17.8 vs 16.3 for Q3W vs weekly vs mitoxantrone (HR 0.79, 95% CI 0.67–0.93; p = 0.004)
Abiraterone				
COU-AA-302 2013, 2014, 2015 [88,109,110]	Abiraterone + prednisone	Placebo + prednisone	No previous DOC ECOG PS 0–1 PSA or RG progression No or mild symptoms, no VMs	FU: 49.2 mo OS 34.7 vs 30.3 mo (HR 0.81; p = 0.0033) rPFS 16.5 vs 8.3 mo (p < 0.0001)
Enzalutamide				
PREVAIL 2014 [89]	Enzalutamide	Placebo	No previous DOC ECOG PS 0–1 PSA or RG progression No or mild symptoms 10% had VMs	FU: 22 mo OS: 32.4 vs 30.2 mo (HR 0.71, 95% CI 0.60–0.84; p < 0.001) rPFS: 20.0 vs. 5.4 mo (HR 0.186, 95% CI 0.15–0.23; p < 0.0001)
SIPULEUCEL-T				
IMPACT 2010 [94]	Sipuleucel-T	Placebo	Some with previous DOC ECOG PS 0–1 No or minimal symptoms	FU: 34.1 mo OS: 25.8 vs 21.7 mo (HR 0.78, 95% CI 0.61–0.98; p = 0.03) PFS: 3.7 vs. 3.6 mo (no difference)
IMPACT 2006 [111]	Sipuleucel-T	Placebo	ECOG PS 0–1 No VMs No corticosteroids	FU: 36 mo OS: 25.9 vs 21.4 mo (p = 0.1) PFS: 11.7 vs 10.0 wk
Ipatasertib				
IPATential150 2021 [96]	Ipatasertib 400 mg/d + abiraterone 1000 mg/d + P5$_{b.i.d.}$	Abiraterone + prednisolone + placebo	Previously untreated for mCRPC No or mild symptoms ± PTEN loss on IHC	rPFS (PTEN loss): 18.5 vs 16.5 mo (HR 0.77, 95% CI 0.61–0.98; p = 0.0335)
Combinations				
PROpel [97,98]	Olaparib 300 mg b.i.d. + abiraterone 1000 mg/d + prednisone 5 mg b.i.d.	Placebo + abiraterone + prednisone	ECOG PS 0–1 Regardless of HRR status (retrospective testing) Prior taxane for mHSPC allowed	ibPFS (ITT): 24.8 vs 16.6 mo (HR 0.66, 95% CI 0.54–0.81; p = 0.001) ibPFS (*BRCA*$^+$): HR 0.24, 95% CI 0.12– 0.45 OS (ITT): 42.1 vs 34.7 mo (HR 0.81, 95% CI 0.67–1.00; p = 0.054) OS (*BRCA*$^+$): NR vs 23.0 mo (HR 0.29, 95% CI 0.14–0.56)
MAGNITUDE [102,112]	Niraparib 200 mg/d + abiraterone 1000 mg/d + P5$_{b.i.d.}$	Placebo + abiraterone 1000 mg/d + P5$_{b.i.d.}$	ECOG PS 0–1 AAP ≤4 mo allowed for mCRPC HRR-biomarker positive cohort Prior DOC 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 *BRCA1/2*$^+$: 19.5 vs 10.9 mo (HR 0.55, 95% CI 0.39–0.78; nominal p = 0.0007)
TALAPRO-2 [104]	Talazoparib 0.5 mg/d + enzalutamide 160 mg/d	Enzalutamide + placebo	ECOG PS 0–1 All-comers: ± HHR deficiency or unknown HRR status Prior AAP/DOC allowed for mHSPC	rPFS (ITT): NR vs 21.9 mo (HR 0.63, 95% CI 0.51–0.78; p < 0.0001) rPFS (*BRCA*$^+$): HR 0.23, 95% CI 0.10–0.53 (p = 0.0002)

AAP = abiraterone acetate + prednisone; ARPI = androgen receptor pathway inhibitor; b.i.d. = twice a day; CI = confidence interval; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; FU = follow-up; HR = hazard ratio; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; ITT = intention-to-treat population; PFS = progression-free survival; ibPFS = imaging-based PFS; rPFS = radiographic PFS; Q3W = every 3 wk; NR = not reached; OS = overall survival; P5$_{b.i.d.}$ = prednisone 5 mg b.i.d.; RG = radiographic; IHC = immunohistochemistry ; HRR = homologous recombination repair; VMs = visceral metastases.

The combination of ARPI plus an PARP inhibitor showed a significant rPFS benefit in RCTs for unselected patients. However, this benefit is mainly driven by homologous recombination repair (HRR)-deficient patients, especially those with *BRCA1/2* alterations. So far, no clear OS benefit has been seen, and the side effects of PARP inhibitors add substantial toxicity to ARPI monotherapy. Therefore, no recommendation is given for patients without HRR or *BRCA1/2* mutations and the data will be re-evaluated after longer follow-up.

3.3.2.1.6.1. AAP plus olaparib. A randomised, double-blind phase 3 trial (PROpel) investigated AAP plus olaparib (300 mg twice daily) or placebo in patients with mCRPC in the first-line setting [97,98]. Patients (n = 796) were randomly assigned 1:1 to the study treatment regardless of HRR gene mutation (HRRm) status, which was retrospectively determined via tumour tissue and circulating tumour DNA tests. The primary endpoint was imaging-based PFS (ibPFS) on investigator assessment. The result was significantly positive in favour of the combination, with ibPFS of 24.8 versus 16.6 mo (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). For the subgroup of patients with positive HRRm status, the HR for rPFS was 0.50 (95% CI 0.34–0.73). Patients with *BRCA* mutation (11% of the ITT population) had an even greater rPFS benefit (HR 0.24, 95% CI 0.12–0.45) and the HR for OS for these patients was 0.30 (95% CI 0.15–0.59), suggesting that the improvement in rPFS observed in the ITT population was primarily driven by patients with a *BRCA* mutation.

The most common AE for patients receiving olaparib plus AAP was anaemia (48%; ≥G3 in 15%; at least one blood transfusion in 18%; multiple transfusions in 12%). Other common AEs were anaemia fatigue (38%), nausea (30%), diarrhoea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%). The combination of olaparib plus AAP was approved by the European Medicines Agency (EMA) for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated [99]. In the USA, the FDA has approved olaparib with AAP for mCRPC patients with deleterious or suspected deleterious *BRCA* mutations as determined via an FDA-approved companion diagnostic test [100].

3.3.2.1.6.2. AAP plus niraparib. A randomised, double-blind, phase 3 trial (MAGNITUDE) evaluated AAP plus niraparib 200 mg once/d or placebo [101]. The study prospectively included two cohorts, an HRR-negative and an HRR-positive cohort. The HRR-negative cohort was closed early because of futility after enrolling 200 patients. In the overall HRR-positive cohort, addition of niraparib to AAP resulted in a significant improvement in the primary endpoint of rPFS in comparison to AAP plus placebo (HR 0.73, 95% CI 0.56–0.96; p = 0.0217), and median rPFS was 16.5 versus 13.7 mo in favour of the combination. In particular, the 113 patients with *BRCA 1/2* mutations who received AAP plus niraparib [102] derived a major rPFS benefit (19.5 vs 10.9 mo; HR 0.55, 95% CI 0.39–0.78; nominal p = 0.0007). The OS data are still immature. 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 *BRCA1/2* mutations in whom chemotherapy is not clinically indicated [103].

3.3.2.1.6.3. Enzalutamide plus talazoparib. A randomised double-blind phase 3 trial (TALAPRO-2) assessed the PARP inhibitor talazoparib (0.5 mg daily) plus enzalutamide versus enzalutamide/placebo as first-line treatment in patients with mCRPC in two cohorts: unselected patients (cohort 1, the all-comer cohort, recruited first) and selected HRR-deficient patients (cohort 2, which completed recruitment after enrolment in cohort 1 finished). The study showed significantly better median rPFS (primary endpoint) in favour of the combination, regardless of HRR pathway status [104]. Median rPFS was not reached for the combination, in contrast to 21.9 mo (95% CI 16.6–25.1) in the control arm. The HR for rPFS was 0.63 (95% CI 0.51–0.78; p < 0.0001). For the subgroups of patients with HRR mutations, the benefit of talazoparib + enzalutamide was much more pronounced, with median rPFS of 27.9 mo (16.6–not reached) in comparison to 16.4 mo (95% CI 10.9–24.6) for the placebo group (HR 0.46, 95% CI 0.30–0.70; p = 0.0003), and HR of 0.70 (95% CI 0.54–0.89; p = 0.0039) in comparison to patients with unknown status or no HRR deficiency. In an exploratory analysis, the HR for rPFS was 0.23 (95% CI 0.10–0.53; p = 0.0002) for patients with *BRCA*-mutated mCRPC, and 0.66 (95% CI 0.39–1.12; p = 0.12) for patients with non-*BRCA* HRR gene–mutated mCRPC in favour of the talazoparib combination [104]. The OS data are still immature. The expected clinical benefit in the subgroups needs to be weighed against the potential burden of side effects.

The most common treatment-emergent AEs with the addition of talazoparib were anaemia, neutropenia, and fatigue; the most common grade 3–4 AE was anaemia (46%), which improved after dose reduction; however, 39% of these patients required a blood transfusion, including 22% who required multiple transfusions, 8% who discontinued treatment because of anaemia, and two patients who were diagnosed with myelodysplastic syndrome/acute myeloid leukaemia [104]. TALAPRO-2 also recruited a HRR-deficient-only cohort (cohort 2; N = 230). The primary analysis for the combined HRR-deficient population (N = 399) met the rPFS endpoint, with a HR of 0.45 (95% CI 0.33–0.61; p < 0.0001; median not reached at the time of analysis for talazoparib vs 13.8 mo for placebo). OS data for this cohort are also immature, but favour talazoparib (HR 0.69, 95% CI 0.46–1.03; p = 0.07) [105].

The FDA approved talazoparib with enzalutamide only for HRR gene–mutated mCRPC [106]. The EMA approved talazoparib with enzalutamide for treatment of patients with mCRPC (with or without gene mutations) in whom chemotherapy is not clinically indicated [107].

Table 7 summarises phase 3 RCTs of first-line treatment for mCRPC [88,89,92–94,96–98,102,104,108–112].

3.3.2.2. Second-line treatment for mCRPC and sequencing

All patients who receive treatment for mCRPC will eventually experience disease progression. There is high-level evidence for second-line treatments after first-line treatment for mCRPC with docetaxel or with ARPI. There is a paucity of high-level data on the sequence of treatments in cases with pretreatment with ARPI and/or docetaxel for mHSPC.

3.3.2.2.1. Cabazitaxel. Cabazitaxel was studied in a large, prospective, randomised phase 3 trial (TROPIC) comparing cabazitaxel plus prednisone versus mitoxantrone plus prednisone in 755 patients with mCRPC that had progressed after or during docetaxel-based chemotherapy [113]. The primary endpoint of OS was significantly longer with cabazitaxel (median 15.1 vs 12.7 mo; $p < 0.0001$).

3.3.2.2.2. Abiraterone acetate after docetaxel. Positive results from the large phase 3 COU-AA-301 trial were reported after median follow-up of 12.8 mo [114] and confirmed by the final analysis [115]. All patients had progressive disease after docetaxel therapy (with a maximum of 2 previous chemotherapeutic regimens). At median follow-up of 20.2 mo, median survival was 15.8 mo in the AAP arm, compared to 11.2 mo in the placebo arm (HR 0.74; $p < 0.0001$).

3.3.2.2.3. Enzalutamide after docetaxel. The AFFIRM study randomised 1199 patients with mCRPC that had progressed after docetaxel treatment in a 2:1 ratio to enzalutamide or placebo [116]. At median follow-up of 14.4 mo, median survival was 18.4 mo in the enzalutamide arm, compared to 13.6 mo in the placebo arm (HR 0.63; $p < 0.001$). Final analysis with longer follow-up confirmed the OS results, despite crossover and extensive postprogression therapies [117]. Enzalutamide was also active in patients with visceral metastases. No significant differences in side effects were observed between the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm.

3.3.2.2.4. Radium-223 after ARPI or both ARPI and docetaxel. The only bone-specific drug associated with a survival benefit is the α-emitter radium-223. In a large phase 3 trial (ALSYMPCA), 921 patients with symptomatic mCRPC who failed or were unfit for docetaxel were randomised to six injections of 50 kBq/kg radium-223 or placebo plus SOC. Radium-223 significantly improved median OS by 3.6 mo (HR 0.70; $p < 0.001$) [118]. The associated toxicity was mild [118]. Owing to safety concerns, use of radium-223 was restricted to after docetaxel and at least one AR-targeted agent [119]. In particular, use of radium-223 in combination with AAP was associated with significant safety risks related to fractures and more deaths. This was most striking for patients without concomitant bone health agents [120], so radium-223 should always be used in combination with bone health agents.

3.3.2.2.5. Rucaparib after ARPI. A phase 3 RCT (TRITON-3) included 405 mCRPC patients with a *BRCA1*, *BRCA2*, or *ATM* alteration and disease progression after second-generation ARPI treatment [121]. Patients were randomised 2:1 to rucaparib 600 mg twice daily or physician's choice of either second-line docetaxel or the ARPI not previously received. The primary endpoint of rPFS in the ITT population was significantly better with rucaparib (median 10.2 vs 6.4 mo; HR 0.61, 95% CI 0.47–0.80; $p < 0.001$). The small subgroup with *ATM* mutation did not derive a benefit. An interim analysis revealed that OS data were immature. The study design allowed for crossover, and 60% of patients received a PARP inhibitor at progression (47% rucaparib). Median rPFS was longer with rucaparib in comparison to both docetaxel (11.2 vs 8.3 mo; HR 0.53, 95% CI 0.37–0.77) and an ARPI (11.2 vs 4.5 mo; HR 0.38, 95% CI 0.25–0.58) as the control. The most frequent AEs with rucaparib were fatigue, nausea, and anaemia, including grade ≥3 anaemia in 24% of patients and at least one blood transfusion in 29% [122]. Rucaparib has been approved by the FDA.

3.3.2.2.6. Olaparib after ARPI. For olaparib after an ARPI, see Section 3.3.2.4.

3.3.2.3. Treatment after docetaxel and one line of hormone treatment

For men with rapid progression on AR-targeted therapy (<12 mo), cabazitaxel is the treatment supported by the best data. CARD, an open-label, randomised phase 3 trial, evaluated cabazitaxel after docetaxel and one ARPI (either AAP or enzalutamide) [86]. It included patients with progression within <12 mo on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS in comparison to another ARPI and reduced the risk of death by 36%. rPFS with cabazitaxel remained superior regardless of the ARPI sequence and whether docetaxel was given before or after the first ARPI.

The choice of further treatment after docetaxel and one line of hormone therapy for mCRPC is open for patients who have a response for >12 mo to first-line abiraterone or enzalutamide [91]. Second-line chemotherapy (cabazitaxel), radium-223 (bone-only metastases), ^{177}Lu–PSMA-617 radioligand therapy, and PARP inhibitors (*BRCA* mutations) are valuable options.

Men previously treated with at least one ARPI or both an ARPI and docetaxel and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA damage repair (DDR) genes showed an 88% response rate to olaparib [123], and a composite response of 54.3% (95% CI 39.0–69.1%) in the 400-mg arm and a response in 18/46 evaluable patients (39.1%, 95% CI 25.1–54.6%) in the 300-mg arm in another confirmatory trial [124].

In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [125,126], and there is evidence of cross-resistance between enzalutamide and abiraterone [127,128].

3.3.2.3.1. PSMA-based therapy. The increasing use of PSMA PET as a diagnostic tracer and the realisation that this identifies a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope that accumulates where the tumour is located (theranostics) [129]. The PSMA therapeutic radioligand supported by the most robust data is ^{177}Lu-PSMA-617 [130].

In TheraP, patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected via ^{68}Ga-PSMA-11 and ^{18}FDG PET/CT imaging, were randomised to receive ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously, every 6 wk for up to 6 cycles) or cabazitaxel (20 mg/m^2 for up to 10 cycles). The primary endpoint of this phase 2 trial was a PSA reduction of at least 50%. The primary endpoint was met in analyses for the ITT population (66% for ^{177}Lu-PSMA-617 vs 37% for cabazitaxel; difference 29%, 95% CI 16–42%; $p < 0.0001$) and by treatment received (66% vs. 44%; difference 23%, 95% CI 9–37%; $p = 0.0016$) [131]. At 36-mo follow-up, the secondary endpoint of OS was similar for patients randomly assigned to ^{177}Lu-PSMA versus cabazitaxel (19.1 vs 19.6 mo; difference −0.5 mo, 95% CI −3.7 to + 2.7; HR 0.97, 95% CI 0.7–1.4; $p = 0.99$) [132].

An open-label phase 3 trial (VISION) compared ^{177}Lu-vipivotid tetraxetan (^{177}Lu-PSMA-617 radioligand therapy) with protocol-permitted SOC (excluding chemotherapy, immunotherapy, radium-223, and investigational drugs) in mCRPC patients with PSMA-expressing metastases on PET/CT who were previously treated with at least one ARPI and one or two taxanes. Imaging-based PFS and OS were the primary endpoints. More than 800 patients were randomised. ^{177}Lu-PSMA-617 plus SOC significantly prolonged imaging-based PFS and OS in comparison to SOC alone. The incidence of grade ≥3 AEs was higher with ^{177}Lu-PSMA-617 (52.7% vs 38.0%), but quality of life was not adversely affected. Thus, ^{177}Lu-PSMA-617 is an additional treatment option for this mCRPC population [133].

A systematic review and updated meta-analysis investigated OS and the proportion of patients with any PSA decrease or a >50% PSA decrease. The review included 69 articles and a total of 4157 patients, and revealed that patients treated with ^{177}Lu-PSMA 617 had a significantly greater response to therapy (≥50% PSA decrease) in comparison to the control arm (OR = 5.33, 95% CI: 1.24–22.90, $p < 0.05$). Meta-analysis revealed that OS was improved after ^{177}Lu-PSMA-617 therapy, with a pooled HR of 0.26 (95% CI 0.18–0.37, $p < 0.00001$) for any PSA decline and 0.52 (95% CI 0.40–0.67; $p < 0.00001$) for a ≥50% PSA decline [134].

3.3.2.3.2. PARP inhibitors for mCRPC. So far, two PARP inhibitors, olaparib and rucaparib, are licensed as monotherapy by the FDA (the EMA has only approved olaparib) and several other PARP inhibitors are under investigation or were approved only in combination with an ARPI (Section 3.3.2.1.6).

A randomised phase 3 trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARPI in mCRPC with alterations in one or more genes with a role in HRR and progression on an ARPI. Most patients were heavily pretreated with one or two chemotherapies and up to two ARPIs [135,136]. The primary endpoint was rPFS on blinded independent central review in the population with *BRCA1/2* or *ATM* mutation (cohort A) and significantly favoured olaparib (HR 0.49, 95% CI 0.38–0.63). The final results for OS demonstrated a significant improvement in cohort A (HR 0.69, 95% CI 0.50– 0.97; $p = 0.0175$). The difference in OS was not significant for men with any (other) HRR alteration (cohort B; HR 0.96, 95% CI 0.63–1.49). Of note, patients in the arm receiving physician's choice of enzalutamide/abiraterone who experienced progression (86/131, 66%) crossed over to olaparib.

Olaparib was approved by the FDA for patients with mCRPC with deleterious or suspected deleterious germline or somatic HRR mutations with progression following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1* and *BRCA2* alterations [99]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib in the second line after ARPI treatment was studied in TRITON 3 and is discussed in Section 3.3.2.2.

ARPI combined with a PARP inhibitor in first-line mCRPC has been studied in several RCTs, including AAP + olaparib [98], AAP + niraparib [102], and enzalutamide + talazoparib [104] (Table 7).

3.3.2.3.3. Platinum chemotherapy. Cisplatin or carboplatin monotherapy and combinations showed limited activity in unselected patients in the predocetaxel era [137]. The combination of cabazitaxel and carboplatin was evaluated in pretreated mCRPC patients in a randomised phase 1/2 trial. The combination improved median PFS from 4.5 mo (95% CI 3.5–5.7) to 7.3 mo (95% CI 5.5–8.2; HR 0.69, 95% CI 0.50–0.95; $p = 0.018$) and was well tolerated [138]. At histopathological and molecular levels, there is preliminary evidence that platinum adds efficacy in patients with aggressive-variant PCa molecular signatures, including *TP53*, *RB1*, and *PTEN* alterations [139].

Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [140], even after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients and patients without DDR gene alterations also showed a 50% PSA decline when treated with platinum in up to 36% of cases [141]. Platinum might be offered to fit patients with advanced mCRPC who harbour DDR gene aberrations after progression on standard treatment options. Prospective controlled trials are ongoing, but there are currently no data to support an improvement in OS.

All the second-line treatment options in this setting are presented in Table 8 [86,113–116,118,121,124,131–133,135,136,142].

3.3.3. Monitoring of treatment

Baseline examinations should include a medical history, clinical examination, blood tests (PSA, total testosterone, full blood count, renal function, liver function, alkaline phosphatase), a bone scan, and CT of the chest, abdomen, and pelvis [143,144]. The utility of choline or PSMA PET/CT scans for progressing CRPC is unclear and this imaging modality is probably not as beneficial as for patients with BCR or hormone-naïve disease. Flares, PSMA upregulation, and discordant results in comparison to a PSA response or progression on ARPI have been described [145]. PSA alone is not reliable enough for monitoring disease activity in advanced CRPC [146] since visceral metastases may develop in men without rising PSA [147]. Instead, the Prostate Can-

Table 8 – Randomised controlled phase 2/3 trials of second-line/third-line treatment for metastatic castration-resistant prostate cancer [a]

Study	Intervention	Comparison	Selection criteria	Main outcomes
Abiraterone				
COU-AA-301 2012 [115]	AAP	Placebo + prednisone	Previous DOC ECOG PS 0–2 PSA or RG progression	FU: 20.2 mo OS: 15.8 vs 11.2 mo (HR 0.74, 95% CI 0.64–0.86; $p < 0.0001$) rPFS no change
COU-AA-301 2011 [114]	As above	As above	As above	FU: 12.8 mo OS: 14.8 vs 10.9 mo (HR 0.65, 95% CI 0.54–0.77; $p < 0.001$) rPFS: 5.6 vs 3.6 mo
Radium-223				
ALSYMPCA 2013 [118]	Radium-223	Placebo	With/without previous DOC ECOG PS 0–2 ≥2 symptomatic BMs, no VMs	OS: 14.9 vs 11.3 mo (HR 0.61, 95% CI 0.46–0.81; $p = 0.002$) All secondary endpoints show a benefit over best SOC
Cabazitaxel				
TROPIC 2013 [142]	Cabazitaxel + prednisone	Mitoxantrone + prednisone	Previous DOC ECOG PS 0–2	OS: 318/378 vs. 346/377 events (OR 2.11, 95% CI 1.33–3.33) OS ≥2 yr: 27% vs 16% (FU: 25.5 mo)
TROPIC 2010 [113]	As above	As above	As above	FU: 12.8 mo OS: 15.1 vs 12.7 mo (HR 0.70, 95% CI 0.59–0.83 $p < 0.0001$) PFS: 2.8 vs 1.4 mo (HR 0.74, 95% CI 0.64–0.86; $p < 0.0001$)
CARD 2019 [86]	Cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	AAP or Enza	Previous DOC Progression ≤12 mo on prior alternative ARPI (before or after DOC)	OS: 13.6 vs 11.0 mo (HR 0.64, 95% CI 0.46–0.89; $p = 0.008$) rPFS: 8.0 vs 3.7 mo (HR 0.54, 95% CI 0.40–0.73; $p < 0.001$) FU: 9.2 mo
Enzalutamide				
AFFIRM 2012 [116]	Enza	Placebo	Previous DOC ECOG PS 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 [124,135,136]	Olaparib	AAP or Enza; crossover allowed at progression	Previous ARPI Alterations in HRR genes	rPFS: 7.39 vs 3.55 mo (HR 0.34, 95% CI 0.25–0.47; $p < 0.0001$) cORR: 33.3% vs 2.3% (OR 20.86, 95% CI 4.18–379.18) OS (*BRCA1/2*, *ATM*): 19.1 vs 14.7 mo (HR 0.69, 95% CI 0.5–0.97; $p = 0.0175$)
TRITON-3 [121]	Rucaparib (600 mg b.i.d.)	DOC or AA or Enza	EOCG PS 0–1 One previous ARPI *BRCA1/2* or *ATM* alteration	rPFS (ITT) 10.2 vs 6.4 mo (HR 0.61, 95% CI 0.47–0.80; $p < 0.001$ for both comparisons)
Radioligand therapy				
VISION 2021 [133]	^{177}Lu-PSMA-617 + SOC	SOC alone	At least previous 1 ARPI and 1–2 taxanes Mandatory: PSMA-positive ^{68}Ga PSMA PET scan	ibFS: 8.7 vs 3.4 mo (HR 0.40, 99.2% CI 0.29–0.57; $p < 0.001$) OS: 15.3 vs 11.3 mo (HR 0.62, 95% CI 0.5–0.74; $p < 0.001$)
TheraP 2021 [131,132]	^{177}Lu-PSMA-617 (8.5 GBq i.v. Q6W, decreasing 0.5 GBq/cycle; up to 6 cycles)	Cabazitaxel (20 mg/m^2 i.v. Q3W, up to 10 cycles)	After DOC Suitable for cabazitaxel	PSA_{50}: 66% vs 37% PSA response (ITT): 66% vs 37% (Δ 29%, 95% CI 16–42%; $p < 0.0001$) PSA response (BTR); 66% vs 44% (Δ 23%, 95% CI 9–37%; $p = 0.0016$) OS: 19.1 vs 19.6 mo (HR 0.97, 95% CI 0.7–1.4; $p = 0.99$)

Δ = difference; AA = abiraterone acetate; AAP = AA + prednisone; ARPI = androgen receptor pathway inhibitor; b.i.d. = twice daily; BMs = bone metastases; BTR = by treatment received; CI = confidence interval; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; Enza = enzalutamide; FU = follow-up; G-CSF = granulocyte colony-stimulating factor; HR = hazard ratio; ITT = intention-to-treat population; i.v. = intravenous; OS = overall survival; OR = odds ratio; cORR = confirmed objective response rate; PSA = prostate-specific antigen; PSA_{50} = reduction in PSA of >50%; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; PFS = progression-free survival; ibPFS = imaging-based PFS; rPFS = radiographic PFS; Q3(6)W = every 3 (6) wk; RG = radiographic; SOC = standard of care; HRR = homologous recombination repair; VMs = visceral metastases.

[a] Only studies reporting survival outcomes as primary endpoints have been included.

cer Clinical Trials Working Group (PCWG)2 guidance recommends a combination of bone scintigraphy and CT scans, PSA measurements, and clinical benefit in assessing men with CRPC [148]. For trial purposes, the updated PCWG3 guidance puts more weight on the importance of documenting progression in existing lesions and introduced the concept of no longer "clinically benefiting" to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment. These recommendations also seem valid for clinical practice outside of trials.

3.3.4. *When to change treatment*

The timing of changes in mCRPC treatment remains a matter of debate, although it is clearly advisable to start or change a treatment immediately in men with symptomatic progressing metastatic disease. Any treatment change should preferably precede development of de novo symptoms or worsening of existing symptoms. Although the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore, it is not clear how to select the most appropriate "second-line" treatment, in particular in patients without HRR alterations or other biomarkers. A positive example, however, is the CARD trial, which clearly established cabazitaxel as a better third-line treatment in docetaxel pretreated patients after one ARPI when compared to use of a second ARPI [86].

The Eastern Cooperative Oncology Group performance status has been used to stratify patients. In general, men with a performance status score of 0–1 are likely to tolerate treatments, and those with a score of >2 are less likely to benefit. However, it is important that treatment decisions are individualised, in particular when symptoms related to disease progression are impacting on performance status. In such cases, a trial of active life-prolonging agents to establish if a given treatment will improve performance status may be appropriate.

3.3.5. *Preventing skeletal-related events*

3.3.5.1. Bisphosphonates. The use of zoledronic acid to reduce skeletal-related events (SREs) has been evaluated in mCRPC. The study was conducted when no active anticancer treatments apart from docetaxel were available. Patients who had CRPC with bone metastases (n = 643) were randomised to receive zoledronic acid (4 or 8 mg every 3 wk for 15 mo) or placebo [149]. The 8-mg dose was poorly tolerated and was reduced to 4 mg, but did not show a significant benefit. However, at 15-mo and 24-mo follow-up, the group treated with 4 mg of zoledronic acid had fewer SREs in comparison to the placebo group (33% vs 44%; p = 0.021) and, in particular, fewer pathological fractures (13.1% vs 22.1%; p = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

3.3.5.2. RANK ligand inhibitors. Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of NFκB ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with greater bone-specific MFS in comparison to placebo (median benefit 4.2 mo; HR 0.85; p = 0.028). This benefit did not translate into a survival difference (43.9 vs 44.8 mo), and neither the FDA nor the EMA has approved denosumab for this indication [150].

The efficacy and safety of denosumab (n = 950) in comparison to zoledronic acid (n = 951) in patients with mCRPC was assessed in a phase 3 trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by the longer time to first on-study SRE (pathological fracture, bone radiation or surgery, or spinal cord compression) of 20.7 versus 17.1 mo (HR 0.82; p = 0.008). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm in comparison to the zoledronic acid arm (p < 0.0001 for both). However, these findings were not associated with any survival benefit, and a post hoc re-evaluation of endpoints demonstrated that denosumab showed identical results when comparing SREs and symptomatic skeletal events [151].

The potential toxicity of these drugs (eg, osteonecrosis of the jaw, hypocalcaemia) must always be kept in mind (5% in M0 CRPC and 8.2% in mCRPC) [152,153]. Patients should have a dental examination before starting therapy, as the risk of jaw necrosis is increased by several risk factors, including a history of trauma, dental surgery, or dental infection [154]. The risk of osteonecrosis of the jaw also increased with the duration of use in a pivotal trial [155] (1 yr vs 2 yr with denosumab), but the difference was not statistically significant in comparison to zoledronic acid. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be avoided via adequate intake of calcium and vitamin D before therapy initiation [156]. Hypocalcaemia should be identified and prevented during treatment using bone-protective agents (the risk of severe hypocalcaemia is 8% with denosumab and 5% with zoledronic acid) [153]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (>500 mg) and vitamin D (>400 IU equivalent) are recommended in all patients, except in cases of hypercalcaemia [153,157,158].

4. Conclusions

The present text is a summary of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines for treatment of relapsing and metastatic prostate cancer. More detailed information and a full list of references are available in the full-text version on the EAU website (http://uroweb.org/guideline/prostate-cancer/).

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