

SPECIAL ARTICLE

Advanced and metastatic prostate cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

K. Fizazi^{1,2}, G. Attard³, A. A. Azad⁴, G. Baciarello⁵, H. Beltran⁶, A. Bjartell⁷, P. Blanchard⁸, F. Bossaert⁹, E. Castro¹⁰, E. Compérat¹¹, J. de Bono¹², A. Deschamps¹³, E. Efstathiou¹⁴, L. Emmett¹⁵, S. Fanti¹⁶, V. Fonteyne¹⁷, A. González-del-Alba¹⁸, G. Gravis¹⁹, N. D. James²⁰, R. Kanesvaran²¹, R. S. McDermott²², N. Mehra²³, C. Parker²⁴, R. M. Renard-Penna²⁵, M. A. Rubin²⁶, F. Saad²⁷, C. Sweeney²⁸, D. Tilki^{29,30,31}, B. Tombal³², A. C. Tree^{12,33}, J. Walz³⁴, T. Zilli^{35,36} & S. Gillessen^{36,37}, on behalf of the ESMO Guidelines Committee*

¹Department of Medical Oncology, Centre Oscar Lambret, Lille; ²Department of Medical Oncology, University of Paris Saclay, Villejuif, France; ³Research Department of Oncology, University College London, London, UK; ⁴Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; ⁵Department of Medical Oncology, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy; ⁶Department of Medical Oncology, Dana Farber Cancer Institute, Boston, USA; ⁷Department of Urology, Skåne University Hospital, Malmö, Sweden; ⁸Department of Radiation Oncology, Gustave Roussy, Université Paris Saclay, INSERM U1018 Oncostat, Villejuif; ⁹CerHom, Villejuif, France; ¹⁰Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; ¹¹Department of Pathology, Medical University of Vienna, Vienna, Austria; ¹²Division of Clinical Studies, The Institute of Cancer Research and Royal Marsden Hospital, London, UK; ¹³Europa Uomo, The European Prostate Cancer Coalition, Antwerp, Belgium; ¹⁴Knight Comprehensive Cancer Center, Oregon Health and Science University, Portland, USA; ¹⁵Department of Theranostics and Nuclear Medicine, St Vincent's Hospital, Sydney, Australia; ¹⁶Department of Nuclear Medicine, IRCCS AOU di Bologna, Bologna, Italy; ¹⁷Department of Radiation Oncology, Ghent University, Ghent, Belgium; ¹⁸Medical Oncology Department, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain; ¹⁹Department of Medical Oncology, Immunity and Cancer Team, Institut Paoli-Calmettes, INSERM, CNRS, CRCM, Aix Marseille University, Marseille, France; ²⁰Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK; ²¹Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; ²²Department of Medical Oncology, St Vincent's University Hospital & University College Dublin, Dublin, Ireland; ²³Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; ²⁴Urology Unit, The Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK; ²⁵Department of Imaging, Hôpital Pitié Salpêtrière, Sorbonne Université, Paris, France; ²⁶Department for Biomedical Research, University of Bern, Bern, Switzerland; ²⁷Department of Surgery and Urologic Oncology, Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montreal, Canada; ²⁸South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, Australia; ²⁹Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg; ³⁰Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; ³¹Department of Urology, Koc University Hospital, Istanbul, Turkey; ³²Division of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ³³Uro-Oncology Department, The Royal Marsden Hospital, Sutton, UK; ³⁴Department of Urology, Institut Paoli-Calmettes Cancer Center, Marseille, France; ³⁵Department of Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona; ³⁶Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano; ³⁷Department of Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland



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INTRODUCTION

This ESMO Clinical Practice Guideline (CPG) focuses on advanced and metastatic prostate cancer. This includes metastatic castration-sensitive prostate cancer (mCSPC), non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-resistant prostate cancer (mCRPC). The management of early-stage disease is covered in the ESMO CPG for local and locoregional prostate cancer.¹

INCIDENCE AND EPIDEMIOLOGY

Information on the incidence and epidemiology of prostate cancer is provided in the ESMO CPG for local and locoregional prostate cancer.¹

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Details regarding the diagnosis, pathology and molecular biology of metastatic prostate cancer are provided in [Supplementary Material Section 1](https://doi.org/10.1016/j.annonc.2026.01.015), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.

Recommendations

- Gleason score reporting is not recommended for mCSPC in case of biopsy of prior radiated tissue or pure neuroendocrine prostate carcinoma (NEPC) [III, E]. Cribriform and intraductal aspects can be considered as Gleason pattern 4 and aggressive [V, B].

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

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- Reporting should generally follow the International Collaboration on Cancer Reporting and World Health Organization recommendations [III, B].
- Grading of metastases (lymph node and distant) is not recommended [III, E].
- Germline testing is recommended in patients with mCSPC [III, A].
 - Panels including cancer susceptibility genes, such as *BRCA1*, *BRCA2*, mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) and *HOXB13*, can be recommended [III, B].
 - Panels including other moderate-risk genes, such as *ATM*, *CHEK2* and *PALB2*, can also be recommended [III, B]. Other genes can be added based on personal and family history [III, B].
- Recommendations on biomarker testing in mCRPC are included in the section 'Management of mCRPC'.

STAGING AND RISK ASSESSMENT

Information on the staging of prostate cancer is provided in the ESMO CPG on local and locoregional prostate cancer.¹ Details regarding risk assessment in mCSPC are provided in [Supplementary Material Section 2](https://doi.org/10.1016/j.annonc.2026.01.015), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.

Recommendations

- Prognosis classifications can be recommended when assessing patients, acknowledging that these are imperfect tools for treatment selection [III, B].

MANAGEMENT OF mCSPC

Management of *de novo* mCSPC

Traditionally, treatment of mCSPC was androgen deprivation therapy (ADT) until progression to castration-resistant prostate cancer (CRPC), at which stage alternative treatments were considered. This paradigm has changed substantially; while ADT remains the backbone of treatment, all patients with mCSPC are now considered for treatment with additional agents alongside ADT, including (at a minimum) androgen receptor pathway inhibitors (ARPIs), unless there are major contraindicating comorbidities. Multiple phase III studies evaluating abiraterone,^{2,3} apalutamide,⁴ darolutamide^{5,6} and enzalutamide^{7,8} have demonstrated the benefit of this approach in terms of progression-free survival (PFS), overall survival (OS) and other clinically important surrogate endpoints.

The addition of six cycles of docetaxel chemotherapy (ChT) to ADT has also been shown to prolong OS in patients with *de novo* mCSPC;^{9,10} however, given the OS benefit of triplet systemic treatment (ADT–docetaxel–ARPI), a docetaxel doublet is typically no longer used, unless an ARPI is not available. The combination of ADT–docetaxel–ARPI has been evaluated in several randomised trials. OS benefit was demonstrated with ADT–docetaxel–abiraterone versus ADT–docetaxel in PEACE-1 [hazard ratio (HR)

0.75, 95.1% confidence interval (CI) 0.59–0.95]¹¹ and with ADT–docetaxel–darolutamide versus ADT–docetaxel in ARASENS (HR 0.68, 95% CI 0.57–0.80);¹² improvements in other endpoints also favoured the triplet regimens.^{11,12} The greatest benefits were reported in patients with *de novo* mCSPC and a high metastatic burden, likely because events occur later in those with a lower metastatic burden, thus requiring longer follow-up. OS benefit was also reported with the addition of enzalutamide to ADT–docetaxel in a prespecified subgroup of patients with synchronous mCSPC in the ENZAMET trial.^{7,13} To date, no prospective, randomised study has evaluated ADT–docetaxel–ARPI versus ADT–ARPI. Until such data are available, either a doublet (ADT–ARPI) or a triplet regimen (ADT, six cycles of docetaxel and an ARPI) should be considered, at least in patients with *de novo* mCSPC and high-volume disease who are fit for such treatment and consent to it.

While the accepted duration of docetaxel treatment is six cycles, treatment with ARPIs has continued in clinical trials until disease progression or unacceptable toxicity. Given the excellent responses associated with these agents and the prognostic value of a reduction in prostate-specific antigen (PSA) to <0.2 ng/ml,^{14–16} there is considerable interest in reducing treatment duration, thereby improving quality of life (QoL) via mitigation of side-effects, although this is currently considered experimental. This approach will be prospectively studied in a pragmatic clinical trial.¹⁷

While maintenance of bone health should be strongly considered in all patients with mCSPC, randomised trials have reported no benefit with intensified monthly dosing of zoledronic acid to prevent skeletal-related events (SREs) in this setting.^{9,18} No data are available for denosumab.

Treatment of the primary tumour in *de novo* mCSPC.

Three phase III randomised trials (HORRAD,¹⁹ STAMPEDE²⁰ and PEACE-1²¹) have compared systemic treatment alone or in combination with radiotherapy (RT) to the primary tumour in mCSPC. Overall, they demonstrated improved PFS but not OS with the combination treatment. In a prespecified subgroup analysis of STAMPEDE, prostate RT was associated with OS benefit only in low-volume disease (HR 0.68, 95% CI 0.52–0.90), although this was not observed in the PEACE-1 study, in which 60% of patients were treated with docetaxel (stratification factor) and 50% were treated with abiraterone by randomisation.^{20,21} PEACE-1 used a factorial 2 × 2 design to evaluate abiraterone and prostate RT in *de novo* mCSPC treated with ADT or ADT–docetaxel as standard of care (SoC).²¹ In patients with low-volume disease, ADT–docetaxel–RT or ADT–docetaxel–abiraterone–RT was associated with improved radiographic PFS (rPFS) versus SoC, but not OS.²¹ In the overall population, irrespective of metastatic burden, prostate RT improved CRPC-free survival and delayed time to serious genitourinary (GU) events ($P = 0.0001$),²¹ thus justifying its use despite the inconsistent impact of RT on OS across the three trials.

An algorithm for the management of *de novo* mCSPC is shown in [Figure 1](#).

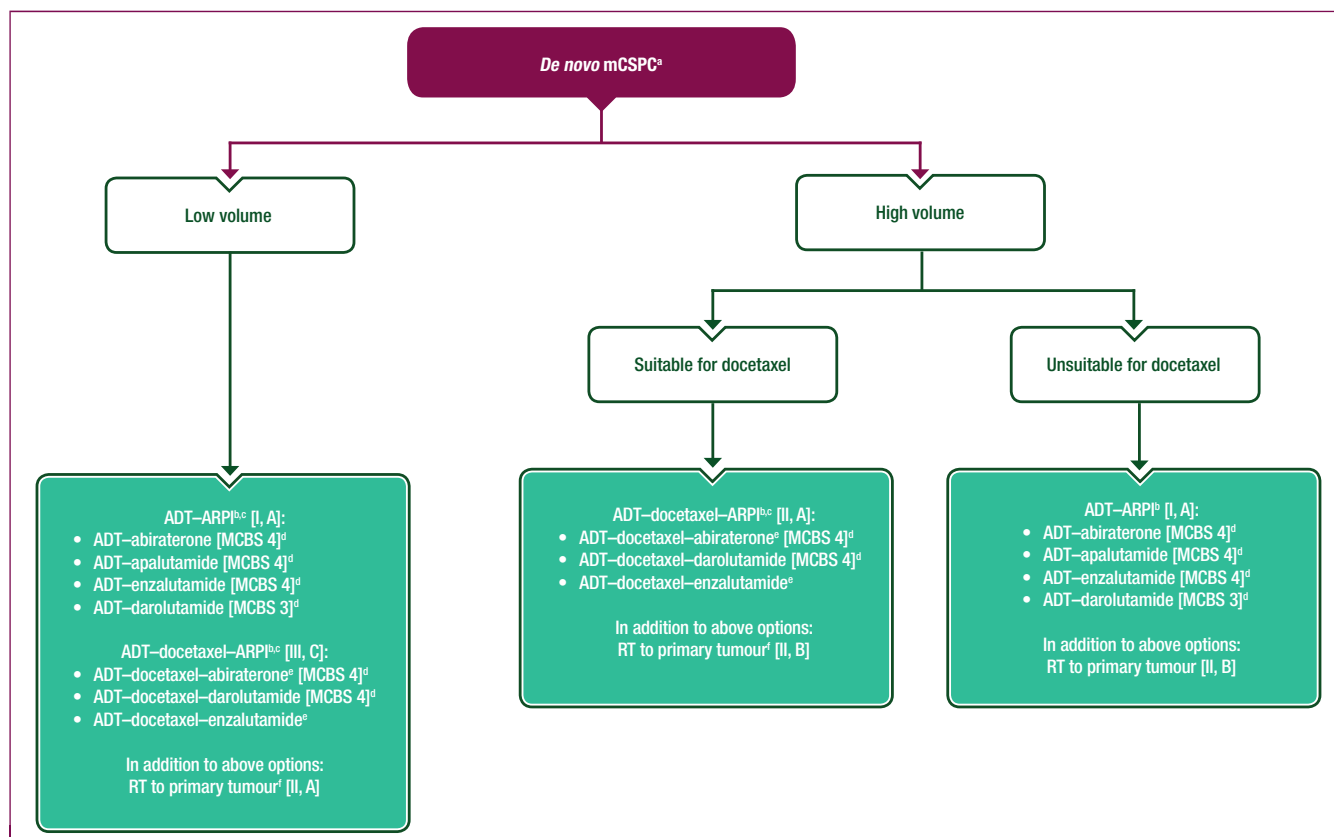


Figure 1. Management of *de novo* mCSPC.

Purple: algorithm title; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mCSPC, metastatic castration-sensitive prostate cancer; RT, radiotherapy.

^aMetastasis-directed therapy remains investigational but can be recommended as an option for selected patients with oligometastatic mCSPC to delay disease progression, especially in the oligorecurrent setting where there are more supporting data [II, B].

^bRecommended duration of treatment is six cycles for docetaxel [III, A], until disease progression for ARPIs [III, A] and lifelong for ADT [III, A]. Individualisation should be discussed on a case-by-case basis, taking into account comorbidities and tolerance [III, A]. ADT monotherapy cannot generally be recommended [I, D] and should only be used in selected unfit patients who have a short life expectancy [I, C].

^cIf an ARPI is not available, ADT-docetaxel is recommended for fit patients [I, A; ESMO-MCBS v2.0 score: 3].

^dESMO-MCBS v2.0¹⁰⁰ was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^eNot EMA or FDA approved.

^fIn patients receiving ADT-docetaxel-ARPI, RT to the prostate should be started when docetaxel treatment is complete [III, A].

Management of relapsed mCSPC after local treatment

Systemic therapy for relapse of previously treated localised prostate cancer is complex. As many patients have oligometastatic or 'low-volume' disease and, thus, a good prognosis,^{22,23} it is not currently clear when systemic treatment, local treatment of metastases, both systemic and local approaches or none of these should be used. In patients with later, slower relapses defined solely on prostate-specific membrane antigen (PSMA)-positron emission tomography (PET)-computed tomography (CT) imaging, there is an additional complication of navigating the relationship between PET-detected metastases and conventional imaging (CT and bone scan) findings.

OS benefits have been reported in subgroup analyses of phase III trials evaluating apalutamide (HR 0.22, 95% CI 0.09-0.55)²⁴ and enzalutamide (HR 0.47, 95% CI 0.28-0.79)¹³ in patients with metachronous and low-volume mCSPC. Adding docetaxel to ADT alone in this population does not appear to provide benefit.²⁵

Patients with the relatively rare scenario of high-metastatic volume relapsed mCSPC probably require long-term ADT and have a similarly poor prognosis to patients with high-volume synchronous disease.^{22,23} Based on data from several trials, these patients can benefit from treatment with ADT-ARPI.^{4,7,26,27} In patients who are fit enough for treatment with docetaxel, ADT-docetaxel-ARPI can be considered as per the ARASENS trial.^{12,28}

The use of intermittent therapy in patients treated with combination therapy including an ARPI is being evaluated in clinical studies.¹⁷

An algorithm for the management of relapsed mCSPC after local treatment is shown in Figure 2.

Metastasis-directed therapy for mCSPC

With the increased implementation of next-generation imaging (NGI), many patients with mCSPC are being diagnosed with oligometastases. Metastasis-directed therapy, usually in the form of stereotactic body RT, has been

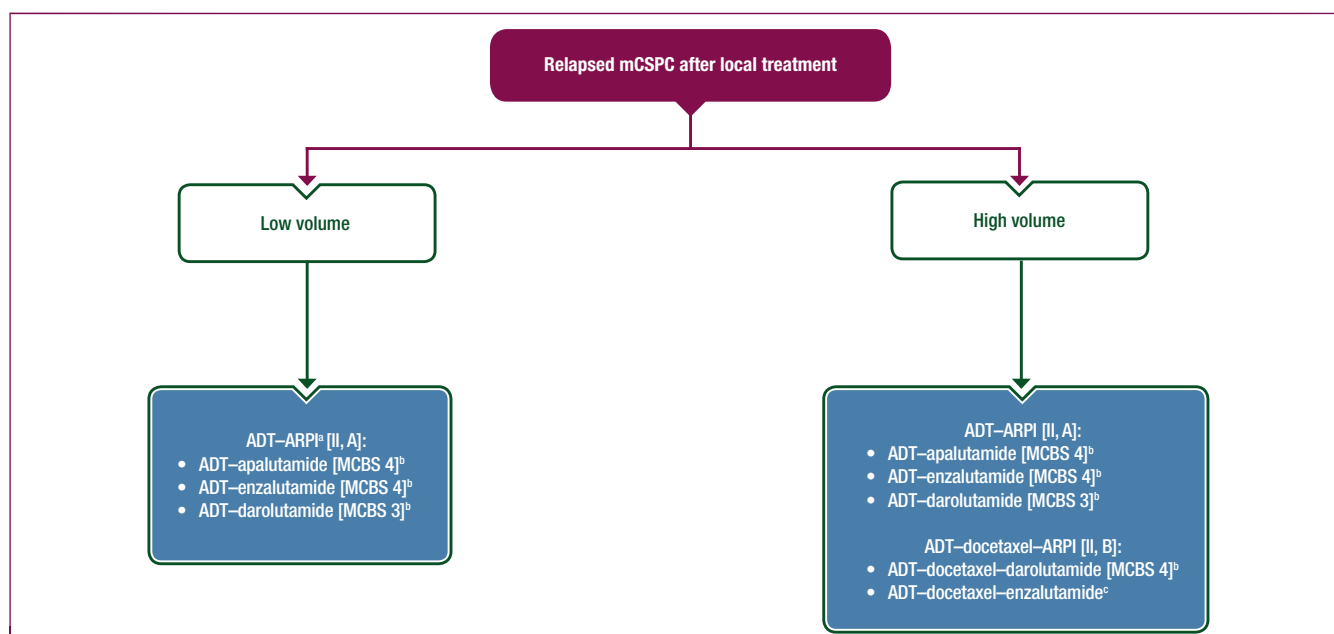


Figure 2. Management of relapsed mCSPC after local treatment.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mCSPC, metastatic castration-sensitive prostate cancer.

^aThe decision to treat with ARPI-ADT should be balanced against life expectancy and comorbidities [II, A].

^bESMO-MCBS v2.0¹⁰⁰ was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^cNot EMA or FDA approved.

increasingly adopted in the management of this patient group, to delay disease progression and potentially improve survival.²⁹⁻³⁴

There is evidence of benefit with metastasis-directed therapy in the metachronous oligorecurrent setting, although none from phase III trials.²⁹ Two randomised phase II studies (STOMP³² and ORIOLE³³) reported improved PSA-based PFS and time to ADT with metastasis-directed therapy compared with observation and delayed ADT. More recently, the phase II EXTEND trial also demonstrated improved PSA-based PFS and eugonadal PFS with metastasis-directed therapy plus intermittent hormonal therapy compared with intermittent hormonal therapy alone.³⁵ In the phase II RADIOSA trial, adding 6 months of ADT to metastasis-directed therapy extended clinical PFS to 32.2 months compared with 15.1 months with metastasis-directed therapy alone (HR 0.43, 95% CI 0.26-0.72).³⁰

Ongoing randomised phase III clinical trials (NCT06320067, NCT03784755, NCT04115007, NCT05209243) are expected to provide conclusive evidence for metastasis-directed therapy in both *de novo* and metachronous mCSPC.

Recommendations

Management of *de novo* mCSPC

- ADT-ARPI is strongly recommended for patients with *de novo* low-volume (by conventional imaging) mCSPC [I, A]. Recommended options are:

- ADT-abiraterone [ESMO-Magnitude of Clinical Benefit Scale (MCBS) v2.0 score: 4]
- ADT-apalutamide (ESMO-MCBS v2.0 score: 4)
- ADT-enzalutamide (ESMO-MCBS v2.0 score: 4)
- ADT-darolutamide (ESMO-MCBS v2.0 score: 3)
- ADT-docetaxel-ARPI may be considered for selected patients with *de novo* low-volume mCSPC who are suitable for docetaxel ChT [III, C]. Options are:
 - ADT-docetaxel-abiraterone [ESMO-MCBS v2.0 score: 4; not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved]
 - ADT-docetaxel-darolutamide (ESMO-MCBS v2.0 score: 4)
 - ADT-docetaxel-enzalutamide (not EMA or FDA approved)
- ADT-docetaxel-ARPI is recommended for patients with *de novo* high-volume mCSPC who are suitable for docetaxel ChT [II, A]. Recommended options are:
 - ADT-docetaxel-abiraterone (ESMO-MCBS v2.0 score: 4; not EMA or FDA approved)
 - ADT-docetaxel-darolutamide (ESMO-MCBS v2.0 score: 4)
 - ADT-docetaxel-enzalutamide (not EMA or FDA approved)
- ADT-ARPI is recommended for patients with *de novo* high-volume disease who are not suitable for docetaxel [I, A]. Recommended options are:
 - ADT-abiraterone (ESMO-MCBS v2.0 score: 4)
 - ADT-apalutamide (ESMO-MCBS v2.0 score: 4)

- ADT—enzalutamide (ESMO-MCBS v2.0 score: 4)
- ADT—darolutamide (ESMO-MCBS v2.0 score: 3)
- RT to the primary tumour combined with systemic treatment is recommended for patients with *de novo* low-volume mCSPC [II, A]. This approach can also be recommended for patients with *de novo* high-volume mCSPC, given its preventive effect on severe GU symptoms [II, B].
 - In patients receiving ADT—docetaxel—ARPI, RT to the prostate should be started when docetaxel treatment is complete [III, A].
- The recommended duration of systemic treatment of *de novo* mCSPC is six cycles for docetaxel [III, A], until disease progression for ARPIs [III, A] and lifelong for ADT [III, A]. Individualisation should be discussed on a case-by-case basis, taking into account response, comorbidities and tolerance [III, A].
- Monthly zoledronic acid or denosumab is not recommended in mCSPC [II, E].
- ADT—docetaxel cannot generally be recommended for mCSPC [I, D]. If an ARPI is not available, ADT—docetaxel is recommended for fit patients with *de novo* mCSPC [I, A; ESMO-MCBS v2.0 score: 3].
- ADT monotherapy cannot generally be recommended [I, D] and should only be used in selected unfit patients who have a short life expectancy [I, C].

Management of relapsed mCSPC after local treatment

- ADT—ARPI is mostly recommended for patients with metachronous low-volume mCSPC [II, A]. Recommended options are:
 - ADT—apalutamide (ESMO-MCBS v2.0 score: 4)
 - ADT—enzalutamide (ESMO-MCBS v2.0 score: 4)
 - ADT—darolutamide (ESMO-MCBS v2.0 score: 3)
- The decision to treat metachronous low-volume mCSPC with ADT—ARPI should be balanced against life expectancy and comorbidities [II, A].
- Docetaxel is not recommended for patients with metachronous low-volume mCSPC [II, E].
- ADT—ARPI is recommended for patients with metachronous high-volume mCSPC [II, A]. Recommended options are:
 - ADT—apalutamide (ESMO-MCBS v2.0 score: 4)
 - ADT—enzalutamide (ESMO-MCBS v2.0 score: 4)
 - ADT—darolutamide (ESMO-MCBS v2.0 score: 3)
- ADT—docetaxel—ARPI can also be recommended for patients with metachronous high-volume mCSPC [II, B]. Recommended options are:
 - ADT—docetaxel—darolutamide (ESMO-MCBS v2.0 score: 4)
 - ADT—docetaxel—enzalutamide (not EMA or FDA approved)

Metastasis-directed therapy in mCSPC

- Metastasis-directed therapy remains investigational but can be recommended as an option for selected patients

with oligometastatic mCSPC to delay disease progression, especially in the oligorecurrent setting where there is more supporting data [II, B].

MANAGEMENT OF nmCRPC

CRPC is defined as disease progression during ADT with serum testosterone at castrate levels (<0.50 ng/ml). nmCRPC is defined as the absence of metastases (M0) on conventional imaging (bone scintigraphy and CT scan). The risk of progression to clinical metastases or death is linked to the Gleason score and PSA doubling time. A PSA doubling time of <10 months is associated with worse outcome and has been used in recent clinical trials as the definition for high-risk nmCRPC.

Patients with nmCRPC were randomised in three phase III studies to receive ADT plus apalutamide, darolutamide or enzalutamide versus ADT—placebo until the appearance of metastases on conventional imaging [bone scan and CT or magnetic resonance imaging (MRI) of the abdomen and chest].^{36–38} The studies reported similar results: apalutamide, darolutamide and enzalutamide significantly improved the primary endpoint of metastasis-free survival (MFS) and, at final analyses, demonstrated significant improvements in OS versus placebo. In the SPARTAN trial, the HR for MFS was 0.28 (95% CI 0.23–0.35)³⁶ and the HR for OS was 0.78 (95% CI 0.64–0.96),³⁹ favouring ADT—apalutamide. In the ARAMIS trial, MFS HR was 0.41 (95% CI 0.34–0.50)³⁷ and OS HR was 0.69 (95% CI 0.53–0.88),⁴⁰ in favour of ADT—darolutamide. In PROSPER, MFS HR was 0.29 (95% CI 0.24–0.35)³⁸ and OS HR was 0.73 (95% CI 0.61–0.89),⁴¹ in favour of ADT—enzalutamide.

The introduction of NGI has impacted the management of nmCRPC, as it offers significantly enhanced sensitivity and specificity compared with conventional imaging, particularly when carried out with PSMA ligands.⁴² PSMA—PET—CT offers superior detection of the extent of disease, often resulting in upstaging.^{42–44}

An algorithm for the management of high-risk nmCRPC is shown in Figure 3.

Recommendations

- NGI (e.g. PSMA—PET) is optional in nmCRPC [III, C].
- ADT—apalutamide (ESMO-MCBS v2.0 score: 4), ADT—darolutamide (ESMO-MCBS v2.0 score: 3) or ADT—enzalutamide (ESMO-MCBS v2.0 score: 3) are recommended for patients with high-risk nmCRPC (defined as a PSA doubling time of <10 months and estimated life expectancy of >5 years), if they have not been used before [I, A].

MANAGEMENT OF mCRPC

Biomarker testing in metastatic CRPC

Details regarding biomarker testing in mCRPC are provided in [Supplementary Material Section 3](https://doi.org/10.1016/j.annonc.2026.01.015), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.

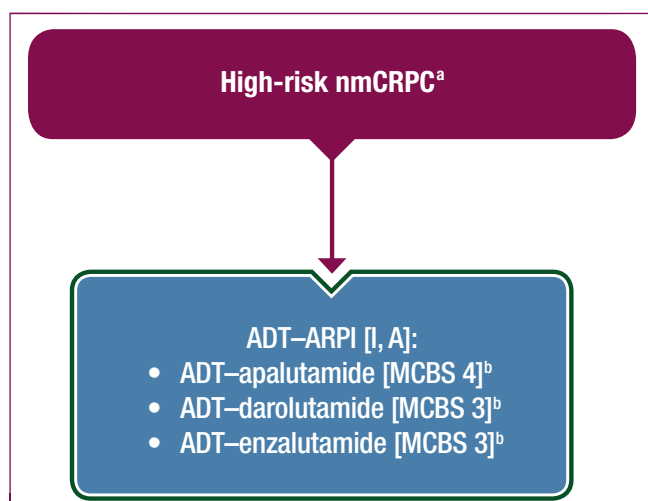


Figure 3. Management of high-risk nmCRPC.

Purple: algorithm title; blue: systemic anticancer therapy or their combination. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

^aPSA doubling time <10 months and estimated life expectancy >5 years.

^bESMO-MCBS v2.0¹⁰⁰ was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

Management of mCRPC without known genetic alterations

An algorithm for the management of mCRPC without known genetic alterations is shown in Figure 4.

Bicalutamide and low-dose corticosteroids demonstrate anticancer activity (PSA and symptomatic responses) in mCRPC, but no OS benefit.^{45,46} Docetaxel was the first agent to demonstrate improved OS in mCRPC. In the TAX 327 trial, docetaxel (75 mg/m² every 3 weeks) combined with prednisone significantly increased OS when compared with mitoxantrone–prednisone (HR 0.76, 95% CI 0.62–0.94).⁴⁷ Similarly, the SWOG-9916 trial showed that docetaxel (60 mg/m² every 3 weeks)—estramustine—prednisone improved OS versus mitoxantrone—prednisone (HR 0.80, 95% CI 0.67–0.97).⁴⁸ In both studies, docetaxel increased the risk of myelosuppression, febrile neutropenia, fatigue, alopecia, diarrhoea, neuropathy and peripheral oedema. A 2-weekly dosing schedule of 50 mg/m² appears at least as effective as a 3-weekly schedule, but with reduced grade 3–4 adverse events (AEs), and may be considered in selected patients.⁴⁹

In patients with mCRPC who had previously received docetaxel, cabazitaxel improved OS compared with mitoxantrone (HR 0.70, 95% CI 0.59–0.83).⁵⁰ Cabazitaxel was associated with increased myelosuppression (including febrile neutropenia) and diarrhoea. A lowered dose of 20 mg/m² reduced febrile neutropenia without compromising OS in a phase III non-inferiority study.⁵¹ A 2-weekly dosing schedule of 16 mg/m² has been shown to reduce the incidence of high-grade neutropenia compared with 25 mg/m² in older patients with mCRPC.⁵²

Also in the post-docetaxel setting, abiraterone—prednisone improved OS versus placebo—prednisone in the COU-AA-301 study (HR 0.74, 95% CI 0.64–0.86).^{53,54} Enzalutamide was also evaluated in this setting and improved OS versus placebo (HR 0.63, 95% CI 0.53–0.75).⁵⁵

In the ALSYMPCA trial, treatment with radium-223 (²²³Ra), a bone-targeted alpha emitter, significantly increased OS (HR 0.70, 95% CI 0.55–0.88) and time to first SRE (HR 0.66, 95% CI 0.52–0.83) compared with placebo in patients with progressive bone-predominant, symptomatic mCRPC.⁵⁶ Side-effects of ²²³Ra included thrombocytopenia (3% grade 3) and diarrhoea (2% grade 3).⁵⁶

In the phase III VISION trial, patients with mCRPC previously treated with ≥1 ARPI and 1–2 taxane regimens and who had one or more PSMA-positive lesion(s) and no PSMA-negative lesions on gallium-68-labelled PSMA—PET were recruited.⁵⁷ Patients treated with lutetium-177 PSMA-617 (¹⁷⁷Lu-PSMA-617) and best SoC had significantly longer PFS (HR 0.40, 99.2% CI 0.29–0.57) and OS (HR 0.62, 95% CI 0.52–0.74) compared with best SoC alone. Common side-effects with ¹⁷⁷Lu-PSMA-617 included fatigue, dry mouth, nausea, anaemia (13% grade 3) and thrombocytopenia (8% grade 3).⁵⁷

Sequencing and combination treatment in mCRPC. Patients with mCRPC have access to a variety of treatment options. While the most effective treatment strategy remains a topic of ongoing investigation, several studies may offer guidance for treatment selection in specific scenarios.

In taxane-naïve asymptomatic or minimally symptomatic patients who are not (or not yet) eligible for ChT, results from two phase III trials have established the roles of two ARPIs. Abiraterone—prednisone was compared with placebo—prednisone in the COU-AA-302 trial and demonstrated improvements in OS (HR 0.81, 95% CI 0.70–0.93) and other endpoints.⁵⁸ The main side-effects were hypokalaemia, hypertension, oedema and cardiac events. Enzalutamide was compared with placebo in the PREVAIL trial and also resulted in improved OS (HR 0.71, 95% CI 0.60–0.84), with fatigue or asthenia and hypertension reported as the most common AEs.⁵⁹ Visceral metastases were an exclusion criterion in the COU-AA-302 trial,⁵⁸ but 204 of 1717 patients (12%) in the PREVAIL trial presented with visceral metastases.⁵⁹ Patients with lung—but not liver—metastases had a better OS (HR 0.59, 95% CI 0.33–1.06), while rPFS was superior in both subgroups.⁶⁰ In the absence of randomised trials directly comparing ARPIs with docetaxel, clinical factors, symptoms, comorbidities, patient preferences and potential side-effects should inform treatment decisions. The effectiveness of docetaxel following ARPI treatment has only been studied in retrospective analyses, with a suggestion that activity is at least partially maintained.^{61–64}

There is compelling evidence suggesting cross-resistance between abiraterone and enzalutamide. Retrospective and prospective studies have indicated that a second ARPI (abiraterone for prior enzalutamide recipients and vice versa) yields only modest efficacy.^{61,65–67} This diminished activity was also observed in the PLATO study, which evaluated

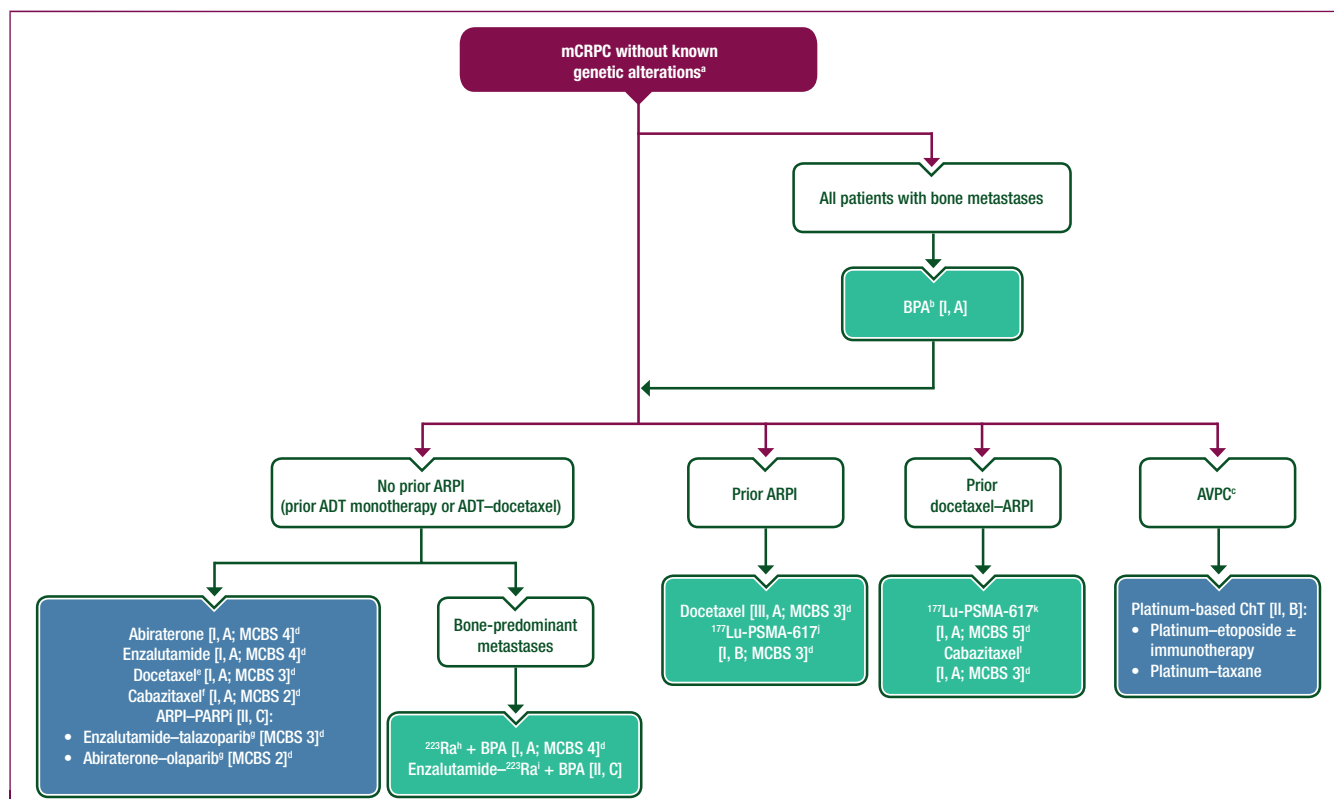


Figure 4. Management of mCRPC without known genetic alterations.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

¹⁷⁷Lu-PSMA-617, lutetium-177 PSMA-617; ²²³Ra, radium-223; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; AVPC, aggressive variant prostate cancer; BPA, bone-protecting agent; ChT, chemotherapy; CT, computed tomography; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mCRPC, metastatic castration-resistant prostate cancer; NEPC, neuroendocrine prostate carcinoma; PARPi, poly (ADP-ribose) polymerase inhibitor; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

^aIn selected patients with oligometastatic mCRPC, metastasis-directed therapy in combination with first-line ARPI can be recommended to delay biochemical and clinical progression [II, B].

^bBPA is administered concomitantly with anticancer treatments.

^cA biopsy to check for histological transformation to NEPC can be recommended for patients who experience rapid progression, especially in the setting of low- or non-rising serum PSA or PSMA-negative progression on PET-CT [III, B].

^dESMO-MCBS v2.0¹⁰⁰ was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^eIf no prior treatment with docetaxel and fit to receive docetaxel.

^fIf prior treatment with docetaxel and fit to receive cabazitaxel.

^gEMA approved, not FDA approved in this setting.

^hIf prior treatment with docetaxel or unfit to receive it, and with no known visceral metastases.

ⁱNot EMA or FDA approved.

^jIn patients with PSMA-positive lesions who are not immediate candidates for docetaxel; FDA approved, not EMA approved.

^kIn patients with one or more PSMA-positive lesion(s) on PSMA-PET and no PSMA-negative lesions; can also be generally recommended in case of intense PSMA uptake and no mismatch with other imaging [II, B].

^lCan also be generally recommended in case of PSMA mismatch with other imaging and/or low PSMA expression [II, B].

abiraterone—enzalutamide versus abiraterone alone after PSA progression on enzalutamide.⁶⁸ The trial did not meet its primary endpoint of rPFS. Cross-resistance appears to be even stronger with abiraterone after prior enzalutamide. There are currently no relevant data available on the sequencing of apalutamide or darolutamide after other ARPIs.

Recently, ¹⁷⁷Lu-PSMA-617 (7.4 GBq every 6 weeks for six cycles) versus an ARPI change (abiraterone or enzalutamide) after an ARPI was evaluated in the phase III PSMAfore trial.⁶⁹ Eligible patients had one or more PSMA-positive lesion(s) and patients randomised to the second ARPI could crossover to ¹⁷⁷Lu-PSMA-617. The primary endpoint of rPFS was met (HR 0.41, 95% CI 0.29-0.56),⁶⁹ and time to worsening

of QoL (HR 0.61, 95% CI 0.50-0.75) and pain (HR 0.72, 95% CI 0.59-0.88) also favoured ¹⁷⁷Lu-PSMA-617.⁷⁰ There was no difference in OS between the groups with high crossover. The incidence of grade ≥ 3 AEs was 36% in the ¹⁷⁷Lu-PSMA-617 group (most commonly anaemia and back pain) versus 48% in the ARPI change group.⁶⁹

The role of ARPI—poly (ADP-ribose) polymerase inhibitor (PARPi) combinations in mCRPC without homologous recombination repair (HRR) alterations remains to be clarified. Based on the demonstrated PFS benefit in patients with mCRPC without alterations, abiraterone—olaparib or enzalutamide—talazoparib are options with unclear clinical benefit, including no demonstration of OS improvement in

this specific subgroup.⁷¹⁻⁷³ Intensification of treatment may, however, significantly increase the risk of AEs, and it is essential to discuss options with the patient and involve them in the decision-making process.

In the randomised phase IV CARD trial, cabazitaxel significantly increased both rPFS (HR 0.54, 95% CI 0.40-0.73) and OS (HR 0.64, 95% CI 0.46-0.89) compared with abiraterone or enzalutamide in patients with docetaxel-pretreated mCRPC who had progression within 12 months on an ARPI, despite 33% of patients in the second ARPI arm crossing over to cabazitaxel.⁷⁴ The main side-effects included haematotoxicity and diarrhoea.

No difference in OS (secondary endpoint) was observed between cabazitaxel and ¹⁷⁷Lu-PSMA-617 in the phase II TheraP trial in patients with docetaxel-pretreated mCRPC with PSMA-positive lesions and no discordance on [¹⁸F]2-fluoro-2-deoxy-D-glucose-PET (of which 91% had received a prior ARPI).⁷⁵ Grade 3-4 AEs were less frequent in the ¹⁷⁷Lu-PSMA-617 arm than in the cabazitaxel arm. As this was a phase II study, caution should be applied when interpreting the results.

No phase III data are currently available for ²²³Ra after progression on an ARPI. The administration of ²²³Ra in combination with abiraterone—prednisone or prednisolone was evaluated in the ERA 223 trial, which reported an increased incidence of fractures among patients receiving this combination (28.6%) versus those receiving abiraterone—prednisone or prednisolone alone (11.4%).⁷⁶ Combining ²²³Ra with enzalutamide improved rPFS (HR 0.69, 95% CI 0.54-0.87) in the PEACE-3 trial, with similar findings for OS (HR 0.69, 95% CI 0.52-0.90) in mostly ARPI-naïve mCRPC. The main AEs included hypertension, fatigue and fractures. Use of a bone-protecting agent (BPA) is, therefore, mandatory with this combination.⁷⁷

mCRPC without prior ARPI treatment. Given that systemic treatment intensification (with an ARPI, with or without docetaxel) is now strongly recommended in earlier settings, it is expected that patients progressing to mCRPC who have only received prior ADT or ADT—docetaxel will become rarer. The treatment for these rare patients is abiraterone or enzalutamide, based on the clear rPFS, OS and QoL benefits of both agents in mCRPC (with or without prior docetaxel).^{53,55,78,79} The choice of abiraterone versus enzalutamide is based on access and patient suitability. There may be clinical settings where alternatives are considered, e.g. abiraterone—PARPi, enzalutamide—PARPi, abiraterone—²²³Ra or enzalutamide—²²³Ra. Carboplatin—cabazitaxel may be an option for patients with evidence of aggressive variant clinical features or neuroendocrine differentiation when hormonal therapy is unlikely to provide benefit.⁸⁰

mCRPC with prior ARPI treatment. This clinical scenario is becoming more frequent, given the cumulative evidence of benefit with ARPIs in CSPC settings. The two main treatment options are docetaxel⁶²⁻⁶⁴ and ¹⁷⁷Lu-PSMA-617.⁶⁹ The role of ²²³Ra in this setting has not been evaluated in randomised trials. Insufficient data are available to

recommend ARPI—²²³Ra or ARPI—PARPi combinations in the post-ARPI mCRPC setting.

Radioisotope rechallenge. Randomised phase III trials of ¹⁷⁷Lu-PSMA-617 have used a standard dose interval and dosing regimen, with six doses (7.4 GBq) administered at 6-week intervals.⁸¹ This regimen was originally derived through dosimetry using external beam dose constraints to the kidneys. Rechallenge with ¹⁷⁷Lu-PSMA-617 has been evaluated in patients who demonstrated disease control and good QoL with standard dosing. In a study of 50 patients undergoing treatment with four doses of ¹⁷⁷Lu-PSMA-617, 15 received rechallenge.⁸² Of these, 11 (73%) had a 50% PSA response to retreatment with a median of two cycles with no added toxicity, although duration of response was more limited with each retreatment cycle.⁸² A multicentre retrospective analysis of 111 patients from German institutions who had received six or more doses of ¹⁷⁷Lu-PSMA-617 evaluated outcomes and toxicity in patients who underwent continuous or rechallenge treatment.⁸³ A median of nine cycles overall was administered in the retreatment patients, and toxicity levels were similar between the two groups.⁸³

Management of aggressive mCRPC variants

Details regarding the treatment of aggressive mCRPC variants are provided in [Supplementary Material Section 4](#), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.

Management of molecularly defined mCRPC subgroups

An algorithm for the management of mCRPC with genetic alterations is shown in [Figure 5](#).

Treatment of mCRPC with BRCA alterations. In the phase III PROfound trial, olaparib was compared with a second ARPI in patients with mCRPC with HRR alterations.^{84,85} Overall, 65% of patients had previously received a taxane.⁸⁵ Olaparib significantly prolonged OS in patients with *BRCA* alterations (HR 0.63, 95% CI 0.42-0.95).⁸⁶ OS benefit and toxicities did not differ by the somatic or germline origin of the alterations. In the phase III TRITON3 study, rucaparib was compared with docetaxel or a second ARPI of the physicians' choice.⁸⁷ In patients with *BRCA* alterations, rucaparib prolonged rPFS compared with docetaxel (HR 0.53, 95% CI 0.37-0.77) or a second ARPI (HR 0.38, 95% CI 0.25-0.58).⁸⁷ The main toxicities for olaparib and rucaparib were haematological AEs and nausea.

Results from three randomised phase III trials (TALAPRO-2,^{72,88} PROPEL^{71,89} and MAGNITUDE^{90,91}) have demonstrated that combining an ARPI with a PARPi as first-line treatment of mCRPC significantly improves outcomes in patients with *BRCA* alterations compared with an ARPI alone. In TALAPRO-2, enzalutamide—talazoparib prolonged rPFS (HR 0.20, 95% CI 0.11-0.36)⁸⁸ and OS (HR 0.47, 95% CI 0.29-0.76)⁹² compared with enzalutamide alone. In PROPEL, abiraterone—olaparib prolonged rPFS versus abiraterone alone (HR 0.24, 95% CI 0.12-0.45)⁹³ and reduced risk of death by 70% (HR 0.29, 95% CI 0.14-0.56).⁷¹ The addition of niraparib to abiraterone in the MAGNITUDE

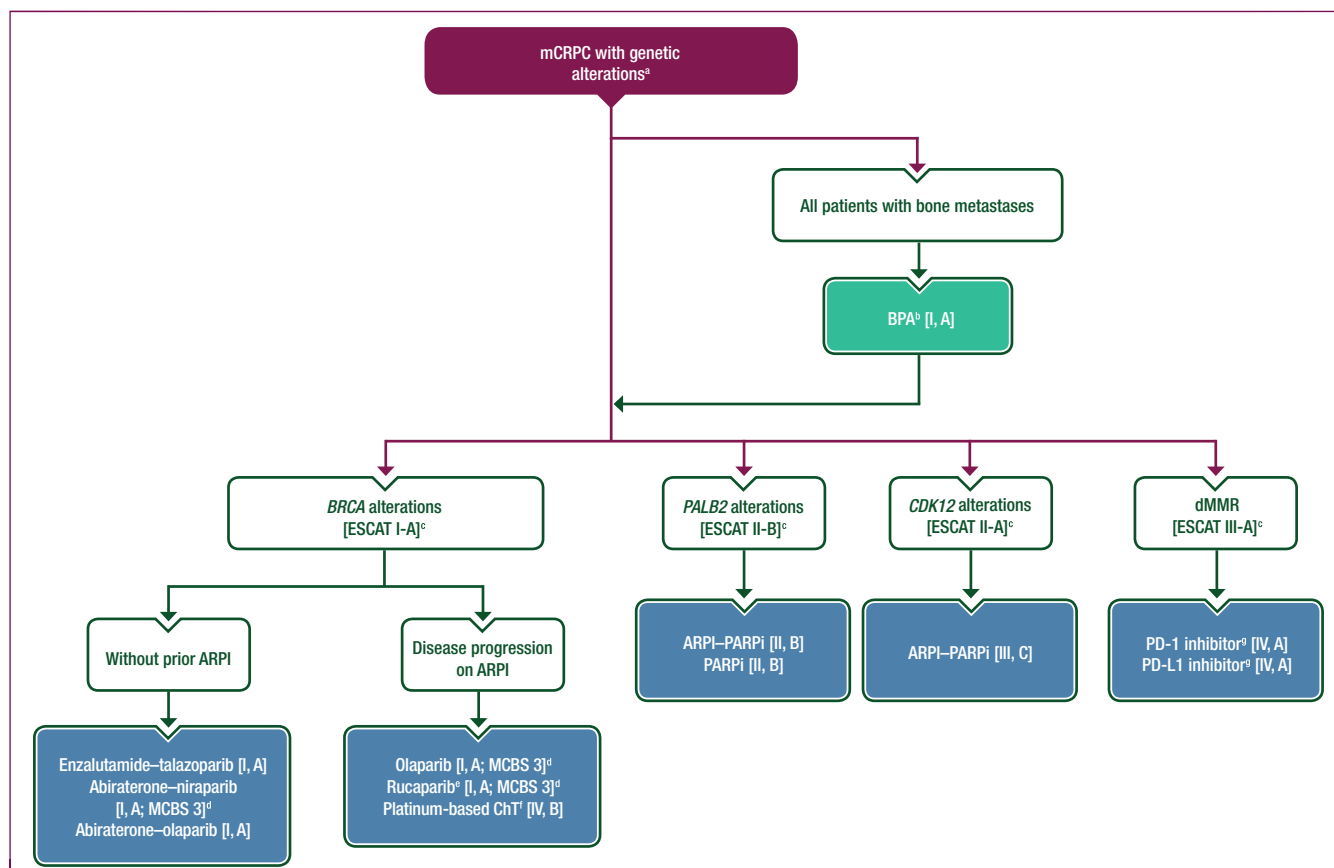


Figure 5. Management of mCRPC with genetic alterations.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

ARPI, androgen receptor pathway inhibitor; BPA, bone-protecting agent; ChT, chemotherapy; dMMR, mismatch repair deficiency; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mCRPC, metastatic castration-resistant prostate cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

^aIn selected patients with oligometastatic mCRPC, metastasis-directed therapy in combination with first-line ARPI can be recommended to delay biochemical and clinical progression [II, B]. Patients with *AR* gene alterations can receive the same treatment as patients without these alterations [III, B]. Patients with loss of suppressor genes (e.g. *TP53*, *PTEN*, *RB1*) can receive the same treatment as patients without these alterations [III, B]; as these patients typically have aggressive disease, close monitoring can be recommended so that opportunities for further treatment are not missed [III, B].

^bBPA^s are administered concomitantly with anticancer treatments.

^cESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.⁹⁹

^dESMO-MCBS v2.0¹⁰⁰ was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^eFDA approved, not EMA approved.

^fCan be considered if a PARPi is not available; a PARPi should be prioritised [III, A].

^gTreatment should begin as soon as possible during the course of disease.

study resulted in significant improvements in rPFS (HR 0.55, 95% CI 0.39–0.78)⁹¹ but not OS (HR 0.788, 95% CI 0.554–1.120).⁹⁴ In these trials, only a limited number of patients had received a prior ARPI for CSPC; therefore, the benefit of ARPI–PARPi over PARPi monotherapy in this population is uncertain.

Retrospective analyses suggest a potential benefit of platinum-based ChT in *BRCA*-mutated prostate cancer,⁹⁵ which is being investigated in ongoing clinical trials.

PARPi in patients with non-*BRCA* alterations. In the MAGNITUDE trial, a preplanned sensitivity analysis of patients with HRR alterations excluding *BRCA1/2*, single *ATM* or

CDK12 alterations and co-occurring *ATM/CDK12* alterations reported a trend toward rPFS benefit with abiraterone–niraparib versus abiraterone–placebo (HR 0.87, 95% CI 0.51–1.49).⁹⁰ In the TALAPRO-2 trial, patients with non-*BRCA* HRR gene alterations had a 34% lower risk of radiographic progression or death with enzalutamide–talazoparib versus enzalutamide–placebo (HR 0.66, 95% CI 0.39–1.12)⁷² but no significant difference was observed in OS.⁹⁶ The FDA carried out a pooled patient-level data analysis of multiple PARPi trials to evaluate the efficacy of PARPi in each HRR-mutated gene.⁹⁷ In addition to *BRCA* alterations, benefit from PARPi was greatest for patients with alterations in *CDK12* (rPFS HR 0.50, 95% CI 0.32–0.80; OS HR 0.63, 95% CI 0.39–0.99) and

PALB2 (rPFS HR 0.52, 95% CI 0.23-1.17; OS HR 0.78, 95% CI 0.34-1.8).⁹⁷ Benefit was not demonstrated for patients with *CHEK2* or *ATM* alterations. Insufficient data are available for analysis of rare HRR alterations such as *RAD51C*, *FANCA* and *NBN* alterations.

Treatment of other molecularly defined subgroups. Information on the treatment of patients with other molecularly defined mCRPC subtypes is provided in [Supplementary Material Section 5](#), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.

Metastasis-directed therapy in mCRPC

The phase II ARTO study demonstrated improved biochemical response rate and PFS when stereotactic body RT was added to abiraterone in patients with oligometastatic mCRPC.⁹⁸

Recommendations

Biomarker testing in mCRPC

- Genomic testing for alterations in *BRCA1* [ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A], *BRCA2* [ESCAT score: I-A], *CDK12* [ESCAT score: II-A] and *PALB2* [ESCAT score: II-B] (at a minimum) is recommended for all patients with CRPC, ideally before the first treatment of mCRPC [III, A].
- Germline testing can be recommended for patients with mCRPC if it has not been carried out previously [III, B].
- MMR deficiency (dMMR) testing is recommended for all patients with mCRPC after ARPI treatment [III, A; ESCAT score: III-A].
- Rebiopsy (to assess neuroendocrine markers and exclude another primary cancer) may be considered in case of dissociation of biochemical versus radiological or clinical features [III, C].

Management of mCRPC without known genetic alterations

- Treatment with a BPA (denosumab or zoledronic acid) is recommended concomitantly in all patients with bone metastases, regardless of the anticancer therapies selected [I, A].
- In patients with mCRPC without an HRR alteration who have not received a prior ARPI:
 - Abiraterone (ESMO-MCBS v2.0 score: 4) or enzalutamide (ESMO-MCBS v2.0 score: 4) are recommended for both taxane-naïve and taxane-pretreated mCRPC [I, A].
 - Docetaxel is recommended in fit patients who have not previously received docetaxel [I, A; ESMO-MCBS v2.0 score: 3].
 - Cabazitaxel is recommended for fit patients who have received prior docetaxel [I, A; ESMO-MCBS v2.0 score: 2].
 - ARPI—PARPi [enzalutamide—talazoparib (ESMO-MCBS v2.0 score: 3; EMA approved, not FDA approved in this setting) or abiraterone—olaparib (ESMO-MCBS

v2.0 score: 2; EMA approved, not FDA approved in this setting)] may be considered for selected patients [II, C].

- In patients with bone-predominant metastases who have not received a prior ARPI:
 - ²²³Ra in combination with a BPA is recommended for patients with no known visceral metastases who have received prior docetaxel or are unfit to receive it [I, A; ESMO-MCBS v2.0 score: 4]. ²²³Ra is not recommended as a single agent for patients with visceral or nodal metastases [III, E].
 - Enzalutamide—²²³Ra in combination with a BPA may be considered [II, C; not EMA or FDA approved].
- In patients with mCRPC without an HRR alteration who have received a prior ARPI:
 - In the absence of other available treatments, docetaxel is preferred over a second ARPI for fit patients [III, A; ESMO-MCBS v2.0 score: 3].
 - ¹⁷⁷Lu-PSMA-617 can be recommended for patients with PSMA-positive lesions who are not immediate candidates for docetaxel [I, B; ESMO-MCBS v2.0 score: 3; FDA approved, not EMA approved].
- In patients with mCRPC without an HRR alteration who have previously received docetaxel—ARPI:
 - ¹⁷⁷Lu-PSMA-617 is recommended for patients with one or more PSMA-positive lesion(s) on PSMA—PET and no PSMA-negative lesions [I, A; ESMO-MCBS v2.0 score: 5]. ¹⁷⁷Lu-PSMA-617 can also be generally recommended in case of intense PSMA uptake and no mismatch with other imaging [II, B; ESMO-MCBS v2.0 score: 5].
 - Cabazitaxel is recommended [I, A; ESMO-MCBS v2.0 score: 3]. Cabazitaxel can also be generally recommended in case of PSMA mismatch with other imaging and/or low PSMA expression (e.g. in liver metastases) [II, B; ESMO-MCBS v2.0 score: 3].
- When docetaxel is indicated for mCRPC, a dose of 50 mg/m² every 2 weeks may be considered for older patients [I, C].

Management of aggressive mCRPC variants

- A biopsy to check for histological transformation to NEPC can be recommended for patients with mCRPC who experience rapid progression, especially in the setting of low- or non-rising serum PSA or PSMA-negative progression on PET—CT [III, B].
- Platinum-based ChT [either platinum—etoposide with or without immunotherapy (based on small-cell lung cancer regimens) or platinum—taxane] can be recommended for patients with aggressive variant prostate cancer with or without NEPC histological features [II, B].

Management of molecularly defined mCRPC subgroups

- Treatment with a BPA (denosumab or zoledronic acid) is recommended concomitantly in all patients with bone metastases, regardless of the anticancer therapies selected [I, A].
- For patients with *BRCA* (germline or somatic) alterations:

- In patients who have not previously received an ARPI, enzalutamide—talazoparib, abiraterone—niraparib (ESMO-MCBS v2.0 score: 3) or abiraterone—olaparib are recommended [I, A].
- In patients who have previously received an ARPI, olaparib (ESMO-MCBS v2.0 score: 3) or rucaparib (ESMO-MCBS v2.0 score: 3; FDA approved, not EMA approved) are recommended [I, A]. A PARPi should be prioritised over docetaxel and a second ARPI in these patients [III, A]. Platinum-based ChT can be considered if a PARPi is not available [IV, B].
- A PARPi (alone or in combination with an ARPI) can be recommended for patients with *PALB2* alterations [II, B].
- ARPI—PARPi may be considered for patients with *CDK12* alterations [III, C].
- A PARPi cannot be recommended for most patients with *CHEK2* or *ATM* alterations [II, D].
- A programmed cell death protein 1 or programmed death-ligand 1 inhibitor is recommended for patients with dMMR; treatment should begin as soon as possible during the course of mCRPC [IV, A].
- Patients with *AR* alterations (e.g. amplifications, mutations) can be offered the same treatment as patients without these alterations [III, B].
- Patients with loss of suppressor genes (e.g. *TP53*, *PTEN*, *RB1*) can be offered the same treatment as patients without these alterations [III, B]. As these patients typically have aggressive disease, close monitoring can be recommended so that opportunities for further treatment are not missed [III, B].

Metastasis-directed therapy in mCRPC

- In selected patients with oligometastatic mCRPC, metastasis-directed therapy in combination with first-line ARPI can be recommended to delay biochemical and clinical progression [II, B].

SUPPORTIVE CARE, FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Details regarding supportive care, symptomatic treatment, palliative care, follow-up and monitoring are provided in [Supplementary Material Section 6](https://doi.org/10.1016/j.annonc.2026.01.015), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.

Recommendations

Supportive care in mCSPC

- Patients receiving ADT should undergo exercise therapy combining aerobic and resistance exercises; this should be supervised for ≥ 12 weeks and then unsupervised beyond that [III, A].
- In patients receiving ADT, especially those with additional risk factors, bone mineral density (BMD) can be assessed via dual-energy X-ray absorptiometry scan; this can be repeated after 12–18 months [III, B].

- Bisphosphonates or denosumab are recommended for patients with low BMD or previous osteoporotic fractures [III, A].
- A daily calcium intake of 700–1200 mg, preferably through diet, and maintenance of serum vitamin D levels above 50 nmol/l are recommended [III, A]. Vitamin D supplementation (800 IU/day) is recommended for patients >50 years [III, A].
- Cardiovascular (CV) health should be monitored in all patients receiving ADT, particularly those with pre-existing CV conditions [III, A].
- Patients with high CV risk should be referred to an expert in cardiology when ADT is considered or started [III, A].

Follow-up in mCSPC

- After ~ 6 months, a protocol including clinical assessment, PSA tests, blood counts and potentially imaging every 3–6 months (or more often in case of detectable PSA defining sub-optimal responses, if needed for detection of specific drug side-effects or for vulnerable, frail patients) is recommended for patients with mCSPC [III, A].
- Imaging (bone and CT scans) should either be carried out at the same frequency as PSA tests or once at 6 months and then repeated only in case of a PSA rise or clinical progression [III, A].
- Serum testosterone assessment is recommended to evaluate ADT effectiveness and to detect castration resistance (e.g. in case of a PSA rise) [III, A].
- PSA level assessment is recommended to evaluate treatment response and disease progression [III, A].

Supportive care, symptomatic treatment and palliative care in mCRPC

- Vitamin D and calcium supplementation are recommended before initiation of a BPA and continuously during treatment [II, A]. Serum calcium should be monitored during treatment [II, A].
- Dental evaluation is recommended before initiation of a BPA, and the BPA should be stopped (at least intermittently) if invasive dental interventions are planned [III, A]. Perioperative antibiotics are recommended in case of dental surgery [III, A].
- BPA treatment should be reviewed after 2–3 years, given the cumulative risk of osteonecrosis of the jaw [III, A].
- A single fraction of external beam RT is recommended for palliation of painful, uncomplicated bone metastases [I, A].
- Whole-spine MRI at a centre with direct access to appropriate imaging facilities is recommended as soon as possible (within 24 hours) for patients with clinical suspicion of metastatic spinal cord compression (MSCC) [I, A].
- Urgent surgery with decompression followed by RT is recommended for patients presenting with single-site MSCC, <48 hours of paraplegia and a life expectancy

of ≥ 3 months [I, A]. In the absence of surgery, urgent RT is recommended [III, A]. High-dose steroids are recommended when symptoms occur [III, A].

- Medical optimisation of bladder function is recommended to support QoL [IV, A].
- Geriatric screening and/or geriatric assessment can be recommended for all older patients (≥ 65 years of age) before initiation of systemic therapy [IV, B].
- Primary prophylaxis with granulocyte colony-stimulating factor to prevent febrile neutropenia can be recommended when using taxanes (docetaxel and cabazitaxel), particularly in older or frail patients [III, B].

Follow-up in mCRPC

- Clinical monitoring with PSA measurements and imaging every 3-6 months (or more frequently as needed) can be recommended [II, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (<https://www.esmo.org/guidelines/esmo-guidelines-methodology>). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Precision Medicine Working Group.⁹⁹ ESMO-MCBS v2.0¹⁰⁰ was used to calculate scores for new therapies/indications approved by the EMA or FDA (<https://www.esmo.org/guidelines/esmo-mcbs>). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in [Supplementary Table S1](#), available at <https://doi.org/10.1016/j.annonc.2026.01.015>.¹⁰¹ Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-advanced-and-metastatic-prostate-cancer>.

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