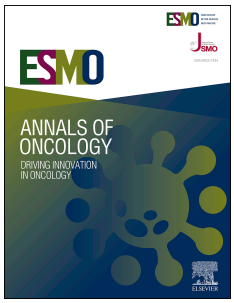

Advanced and metastatic prostate cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

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

K. Fizazi[1,2], G. Attard[3], A.A. Azad[4], G. Baciarello[5], H. Beltran[6], A. Bjartell[7], P. Blanchard[8], F. Bossaert[9], E. Castro[10], E. Compérat[11], J. de Bono[12], A. Deschamps[13], E. Efstathiou[14], L. Emmett[15], S. Fanti[16], V. Fonteyne[17], A. González-del-Alba[18], G. Gravis[19], N.D. James[20], R. Kanesvaran[21], R.S. McDermott[22], N. Mehra[23], C. Parker[24], R.M. Renard-Penna[25], M.A. Rubin[26], F. Saad[27], C. Sweeney[28], D. Tilki,[29,30,31] B. Tombal[32], A.C. Tree[12,33], J. Walz[34], T. Zilli[35,36] & S. Gillessen[36,37], on behalf of the ESMO Guidelines Committee*

[1]Department of Medical Oncology, Centre Oscar Lambret, Lille; [2]Department of Medical Oncology, University of Paris Saclay, Villejuif, France; [3]Research Department of Oncology, University College London, London, UK; [4]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [5]Department of Medical Oncology, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy; [6]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, USA; [7]Department of Urology, Skåne University Hospital, Malmo, Sweden; [8]Département de Radiothérapie Oncologique, Gustave Roussy, Université Paris Saclay, INSERM U1018 Oncostat, Villejuif; [9]CerHom, Villejuif, France; [10]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [11]Department of Pathology, Medical University of Vienna, Vienna, Austria; [12]Division of Clinical Studies, The Institute of Cancer Research and Royal Marsden Hospital, London, UK; [13]Europa Uomo, The European Prostate Cancer Coalition, Antwerp, Belgium; [14]Knight Comprehensive Cancer Center, Oregon Health and Science University, Portland, USA; [15]Department of Theranostics and Nuclear Medicine, St Vincent's Hospital, Sydney, Australia; [16]Department of Nuclear Medicine, IRCCS AOU di Bologna, Bologna, Italy; [17]Department of Radiation Oncology, Ghent University, Ghent, Belgium; [18]Medical Oncology Department, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain; [19]Department of Medical Oncology, Immunity and Cancer Team, Institut Paoli-Calmettes, INSERM, CNRS, CRCM, Aix Marseille University, Marseille, France; [20]Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK; [21]Division of Medical Oncology, National Cancer Centre Singapore, Singapore; [22]Department of Medical Oncology, St

Vincent's University Hospital & University College Dublin, Dublin, Ireland; [23]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [24]Urology Unit, The Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK; [25]Department of Imagery, Hôpital Pitié Salpétrière, Sorbonne Université, Paris, France; [26]Department for Biomedical Research, University of Bern, Bern, Switzerland; [27]Department of Surgery and Urologic Oncology, Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montreal, Canada; [28]South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, Australia; [29]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg; [30]Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [31]Department of Urology, Koc University Hospital, Istanbul, Turkey; [32]Division of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [33]Uro-Oncology Department, The Royal Marsden Hospital, Sutton, UK; [34]Department of Urology, Institut Paoli-Calmettes Cancer Center, Marseille, France; [35]Department of Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona; [36]Faculty of Biomedical Sciences, Università della Svizzera Italian, Lugano; [37]Department of Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland

*_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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Key words: advanced prostate cancer, castration resistant, castration sensitive, diagnosis, guideline, treatment

Highlights (online only):

- This ESMO Clinical Practice Guideline provides key recommendations and algorithms for managing advanced prostate cancer.
- The guideline covers diagnosis, treatment and supportive care.
- Algorithms for the management of metastatic castration-sensitive and castration-resistant prostate cancer are provided.
- The authors are multidisciplinary experts from different institutions in Europe, North America, Asia and Australia.
- Recommendations are based on available scientific data and the authors' collective expert opinion.

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**.

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].
- 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**.

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 for 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] STAMPEDE[20] and PEACE-1[21]) 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 x 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.**

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 increasingly adopted in the management of this patient group, to delay disease progression and potentially improving 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 (STOMP[32] and ORIOLE[33]) 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 (MCBS v2.0 score: 4)
  - ADT–enzalutamide (MCBS v2.0 score: 4)
  - ADT–darolutamide (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 [MCBS v2.0 score: 4; not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved]
  - ADT–docetaxel–darolutamide (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 (MCBS v2.0 score: 4; not EMA or FDA approved)
  - ADT–docetaxel–darolutamide (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 (MCBS v2.0 score: 4)
  - ADT–apalutamide (MCBS v2.0 score: 4)

  - ADT–enzalutamide (MCBS v2.0 score: 4)
  - ADT–darolutamide (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 for *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; 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 (MCBS v2.0 score: 4)
  - ADT–enzalutamide (MCBS v2.0 score: 4)
  - ADT–darolutamide (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 (MCBS v2.0 score: 4)
    - ADT–enzalutamide (MCBS v2.0 score: 4)
    - ADT–darolutamide (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 (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 (MCBS v2.0 score: 4), ADT–darolutamide (MCBS v2.0 score: 3) or ADT–enzalutamide (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**.

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/m^2 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/m^2 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/m^2 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/m^2 reduced febrile neutropenia without compromising OS in a phase III non-inferiority study.[51] A 2-weekly dosing schedule of 16 mg/m^2 has been shown to reduce the incidence of high-grade neutropenia compared with 25 mg/m^2 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 (^{223}Ra), 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 ^{223}Ra 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 ≥1 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 (^{177}Lu-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 ^{177}Lu-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-naive 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 to 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 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, ^{177}Lu-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 ≥1 PSMA-positive lesion(s) and patients randomised to the second ARPI could crossover to ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-PSMA-617 in the phase II TheraP trial in patients with docetaxel-pretreated mCRPC with PSMA-positive lesions and no discordance on [^{18}F]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 ^{177}Lu -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 ^{223}Ra after progression on an ARPI. The administration of ^{223}Ra 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 ^{223}Ra 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-naive 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–^{223}Ra or enzalutamide–^{223}Ra. 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 docetaxel[62-64] and ^{177}Lu -PSMA-617.[69] The role of ^{223}Ra in this setting has not been evaluated in randomised trials. Insufficient data are available to recommend ARPI–^{223}Ra or ARPI–PARPi combinations in the post-ARPI mCRPC setting.

Radioisotope rechallenge. Randomised phase III trials of ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ≥6 doses of ^{177}Lu-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**.

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 for mCPRC 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 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**.

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 for 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 (MCBS v2.0 score: 4) or enzalutamide (MCBS v2.0 score: 4) are recommended for both taxane-naive and taxane-pretreated mCRPC [I, A].

    - Docetaxel is recommended in fit patients who have not previously received docetaxel [I, A; MCBS v2.0 score: 3].

    - Cabazitaxel is recommended for fit patients who have received prior docetaxel [I, A; MCBS v2.0 score: 2].

    - ARPI–PARPi [enzalutamide–talazoparib (MCBS v2.0 score: 3; EMA approved, not FDA approved in this setting) or abiraterone–olaparib (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:

    - ^{223}Ra 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; MCBS v2.0 score: 4]. ^{223}Ra is not recommended as a single agent for patients with visceral or nodal metastases [III, E].

    - Enzalutamide–^{223}Ra 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; MCBS v2.0 score: 3].

- ^{177}Lu-PSMA-617 can be recommended for patients with PSMA-positive lesions who are not immediate candidates for docetaxel [I, B; MCBS v2.0 score: 3; FDA approved, not EMA approved].

- In patients with mCRPC without an HRR alteration who have previously received docetaxel–ARPI:

  - ^{177}Lu-PSMA-617 is recommended for patients with ≥1 PSMA-positive lesion(s) on PSMA-PET and no PSMA-negative lesions [I, A; MCBS v2.0 score: 5]. ^{177}Lu-PSMA-617 can also be generally recommended in case of intense PSMA uptake and no mismatch with other imaging [II, B; MCBS v2.0 score: 5].

  - Cabazitaxel is recommended [I, A; 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; MCBS v2.0 score: 3].

- When docetaxel is indicated for mCRPC, a dose of 50 mg/m^2 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 (MCBS v2.0 score: 4; FDA approved, not EMA approved in this setting), abiraterone–niraparib (MCBS v2.0 score: 3) or abiraterone–olaparib (MCBS v2.0 score: 2; FDA approved, not EMA approved in this setting) are recommended [I, A].

    - In patients who have previously received an ARPI, olaparib (MCBS v2.0 score: 3) or rucaparib (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**.

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) 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 v2.0[100] 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**.[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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AGdA reports personal fees for advisory board membership from Advanced Accelerator Applications, AstraZeneca, Bayer, BMS, Eisai, EUSA Pharma, Janssen, MSD, Novartis, Pfizer and Veracyte; personal fees as an invited speaker from Astellas, Casen Recordati, Ipsen, Merck and Pfizer; personal fees for a writing engagement from Bayer; personal fees for expert testimony from Roche; an institutional research grant from AstraZeneca; travel and accommodation expenses from AstraZeneca, Bayer, Casen Recordati, Ipsen, Merck, MSD and Roche; a non-remunerated role as past member (until 2021) of the Board of Directors for the Spanish Society of Medical Oncology; non-remunerated roles as member of the Board of Directors and President of the Spanish Oncology Genitourinary Group.

GG reports personal travel expenses from Amgen, AstraZeneca, Bayer, BMS, MSD and Novartis/Advanced Accelerator Applications; institutional fees for advisory board membership from Astellas, AstraZeneca, Bayer, BMS, Curium, Eisai, Gilead, Ipsen, Janssen and Pfizer; and institutional fees as an invited speaker from Amgen, AstraZeneca, Bayer, BMS, Ipsen, Janssen, MSD and Novartis/Advanced Accelerator Applications.

NDJ reports personal fees for advisory board membership from AstraZeneca (PARP inhibitors), Bayer (novel hormone therapies for prostate cancer), Clovis (prostate cancer therapies), Janssen (prostate cancer therapies), Merck (bladder cancer therapy), Novartis (prostate cancer therapies) and Sanofi (docetaxel); personal fees as an invited speaker from MSD UK (lectures on therapy for advanced prostate cancer in Brazil, August 2022) and Novartis (^{177}Lu-PSMA-617 at conference in Sao Paulo); institutional fees for expert testimony from Janssen (submission support regarding licensing for abiraterone) and Sanofi (providing STAMPEDE trial data to facilitate licence extensions internationally for docetaxel); and institutional funding as coordinating PI from Astellas (STAMPEDE trial), AstraZeneca (RAD-IO trial in bladder cancer), Janssen (STAMPEDE trial) and Novartis (^{177}Lu-PSMA-617 comparison in STAMPEDE2 trial).

RK reports institutional advisory board membership from Amgen, AstraZeneca, Bayer, BMS, Ferring, Ipsen, Johnson & Johnson, MSD and Pfizer; institutional fees as an invited speaker from Amgen, Astellas, AstraZeneca, BMS, Ipsen, Johnson & Johnson, Merck, MSD, Novartis and Sanofi; institutional research grants from Eisai, Johnson & Johnson and Sanofi; and non-remunerated leadership roles for the International Kidney Cancer Coalition, Singapore Society of Oncology (past President), Singapore Cancer Society (Vice Chairman) and the International Society of Geriatric Oncology (past President).

RSM reports personal fees for advisory board membership from Amgen, Bayer, BMS, Janssen and Pfizer; personal fees as an invited speaker from Astellas, Ipsen, Merck Serono and MSD; institutional fees as local PI for Astellas, Bayer, BMS and Regeneron; and institutional fees as coordinating PI for MSD.

NM reports personal fees for advisory board membership from Astellas, AstraZeneca, Johnson & Johnson, MSD and Pfizer; personal fees as an invited speaker from Ismar Healthcare and Medscape; personal funding from Janssen; institutional fees for advisory board membership from Bayer and Janssen; institutional fees as an invited speaker from Johnson & Johnson, Bureau Prevents and Travel Congress Management B.V.; institutional research grant from AstraZeneca, BMS and EUROSTAR; institutional funding from Astellas, Janssen and Pfizer; institutional fees as coordinating PI from BMS and Janssen; non-remunerated PI for the Prospective Bladder Cancer Infrastructure (Netherlands); and non-remunerated roles as member of the ESMO Faculty (GU, Prostate) and member of the ESMO Publishing Working Group (2014-2023).

CP reports personal fees for Independent Data Monitoring Committee (IDMC) membership from Telix; and institutional fees for advisory board membership from Janssen and Novartis.

RMR-P reports personal fees as an invited speaker from Bayer, Bracco, Ipsen and Janssen; and personal fees for expert testimony from Incepto.

MAR reports personal fees for scientific advisory board membership from NeoGenomics; personal stocks/shares in Owkin and Verintas Therapeutics; a non-renumerated role as PI for a research project supported by Roche; and a non-remunerated research collaboration with Genentech.

FS reports personal fees for advisory board membership from Astellas, AstraZeneca, Bayer, BMS, Janssen, Merck, Novartis, Pfizer and Sumitomo; institutional fees as local PI for Astellas, Bayer, BMS, Janssen, Merck, Novartis, Pfizer and Sanofi; institutional fees as coordinating PI for AstraZeneca; and non-remunerated roles as PI for AbbVie, AstraZeneca, Bayer and Novartis.

CS reports personal fees for advisory board membership from AdvanCell, Astellas, Bayer, BMS, Genentech/Roche and Pfizer; personal fees for consultancy from AdvanCell, Amgen, Astellas, Bayer, Genentech/Roche, Janssen, Novartis and Pfizer; personal stocks/shares from AdvanCell and Perthera; institutional licensing

fees from Exelixis; and institutional research grants from Astellas, Bayer, Dendreon, Janssen, Pfizer and Sanofi.

DT reports personal fees for advisory board membership from A3P Biomedical, Astellas, AstraZeneca, Bayer, Novartis, Pfizer, Roche and Veracyte; personal fees as an invited speaker from Amgen, Apogepha, Ipsen, Janssen and Takeda; and an institutional research grant from Janssen.

BT reports personal fees for advisory board membership from Amgen, Astellas, AstraZeneca, Bayer, Janssen, MSD, Myovant, Novartis, Pfizer and Sanofi; personal fees as an invited speaker from Accord, Amgen, Astellas and Ferring; personal fees for expert testimony from Astellas; a non-remunerated role as past president of the Board of Directors for the European Organisation of Research and Treatment of Cancer (EORTC); and a non-remunerated role as member of the Board of Directors for the International Society for the Study and Exchange of Evidence from Clinical Research and Medical Experience.

ACT reports personal fees as an invited speaker from Astellas, Bayer, Elekta and Janssen; personal fees for role as GU Editor of the *International Journal of Radiation Oncology Biology Physics* (*IJROBP*); institutional fees as an invited speaker from Accuray; institutional research grants from Accuray, Artera, Elekta and Varian; institutional fees as consortium steering committee chair for Elekta; non-remunerated role as an editorial team leader for *IJROBP*; non-remunerated advisory role for the Prostate Cancer UK Clinical Advisory Committee; and non-remunerated member of the American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology (ESTRO).

JW reports institutional fees for advisory board membership from Janssen and Telix; institutional fees as an invited speaker from Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Curium, Intuitive, Ipsen, Janssen and Novartis; institutional funding for expert testimony from Intuitive; other institutional funding from Exact Imaging and Janssen; and a non-remunerated leadership role for the EAU.

TZ reports personal fees as an invited speaker from EAU, European Multidisciplinary Congress on Urological Cancers (EMUC) and ESMO; personal travel expenses from

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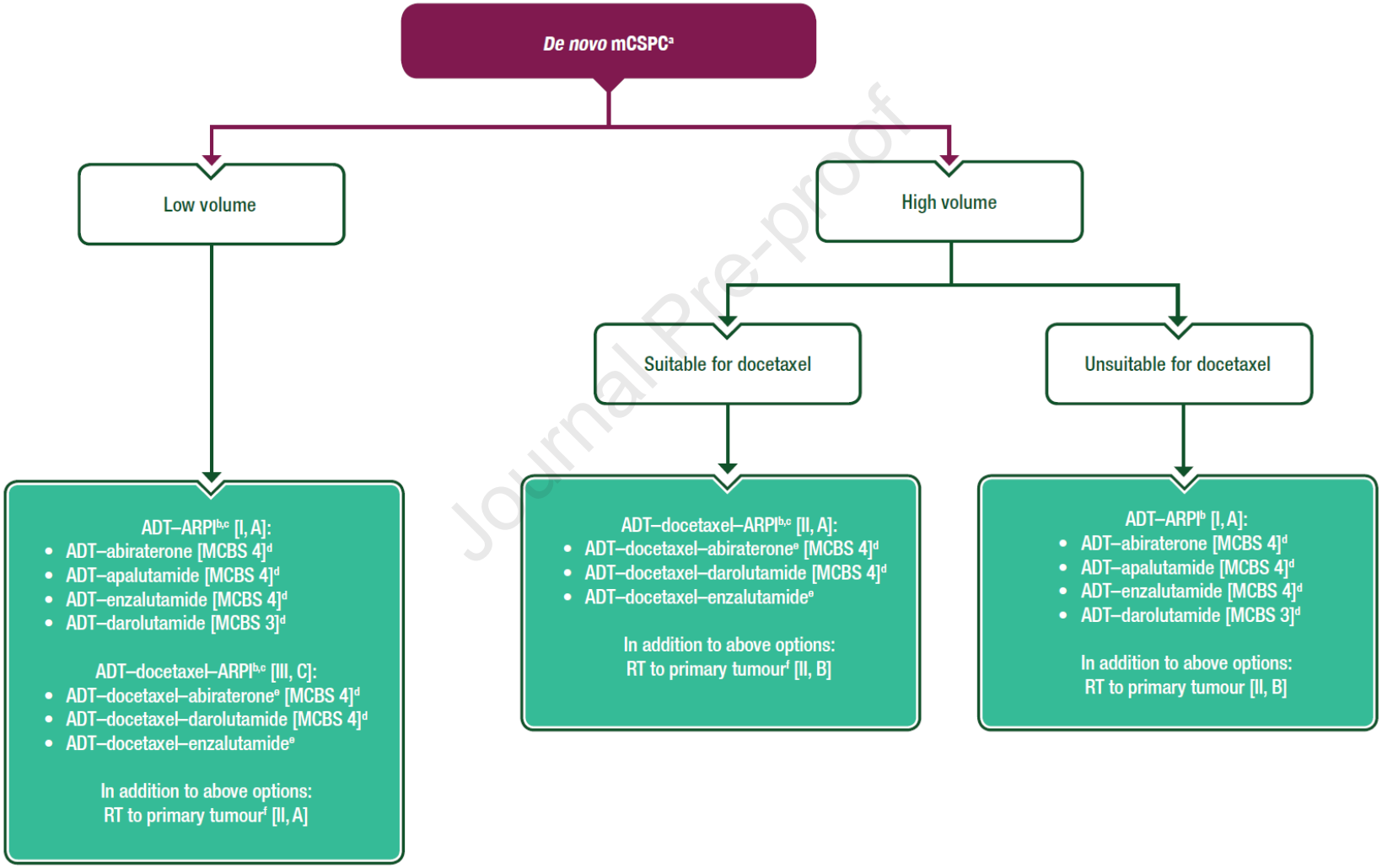
FIGURES

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.

[a]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].

[b]Recommended 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].

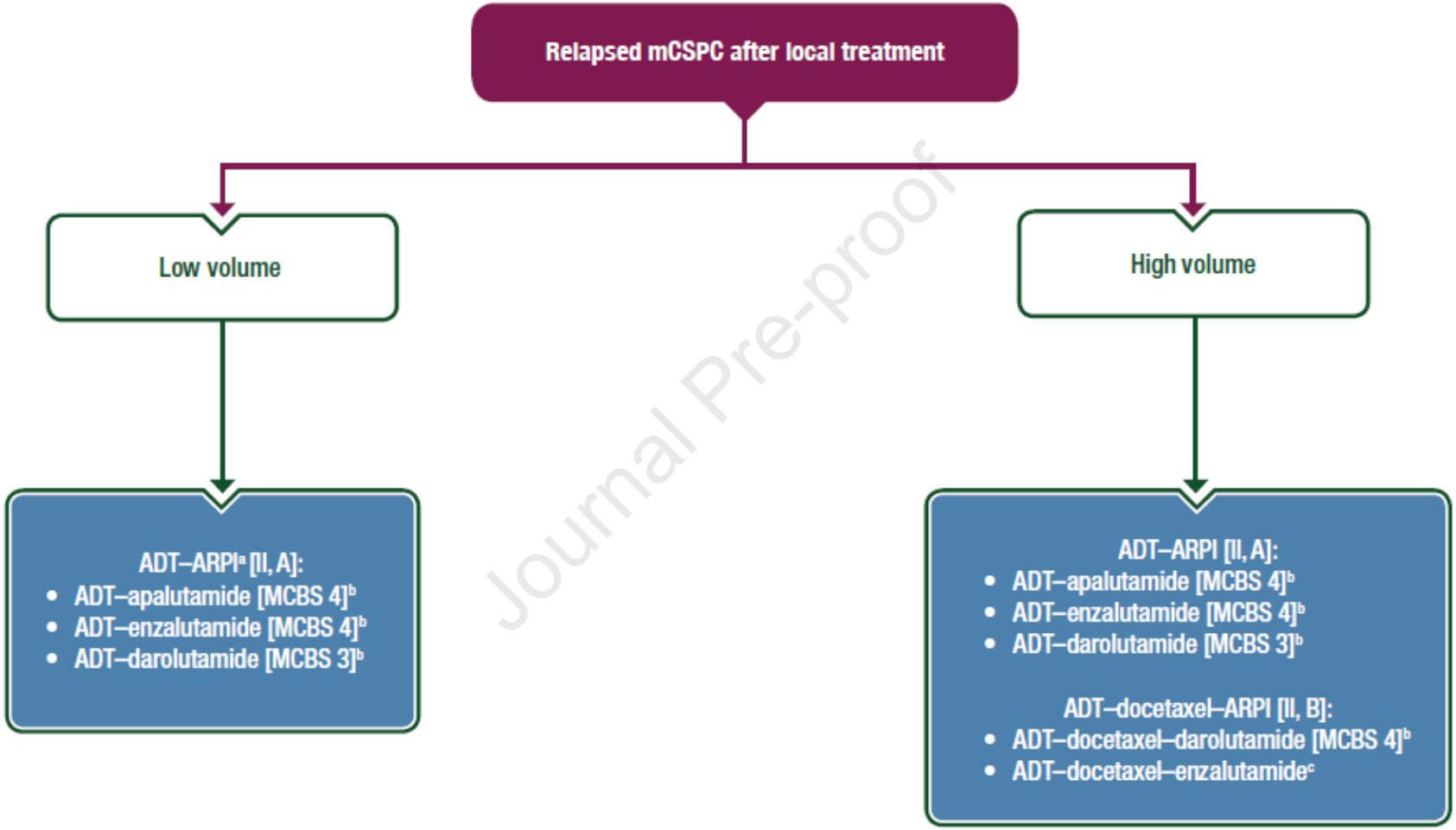
[c]If an ARPI is not available, ADT–docetaxel is recommended for fit patients [I, A; MCBS v2.0 score: 3].

[d]ESMO-MCBS v2.0[100] 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).

[e]Not EMA or FDA approved.

[f]In patients receiving ADT–docetaxel–ARPI, RT to the prostate should be started when docetaxel treatment is complete [III, A].

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.

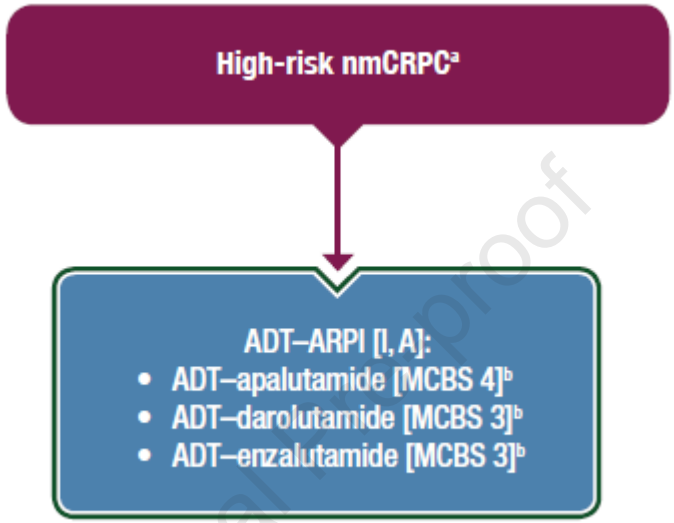
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mCSPC, metastatic castration-sensitive prostate cancer.

[a]The decision to treat with ARPI–ADT should be balanced against life expectancy and comorbidities [II, A].

[b]ESMO-MCBS v2.0[100] 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).

[c]Not EMA or FDA approved.

Figure 3. Management of high-risk nmCRPC.



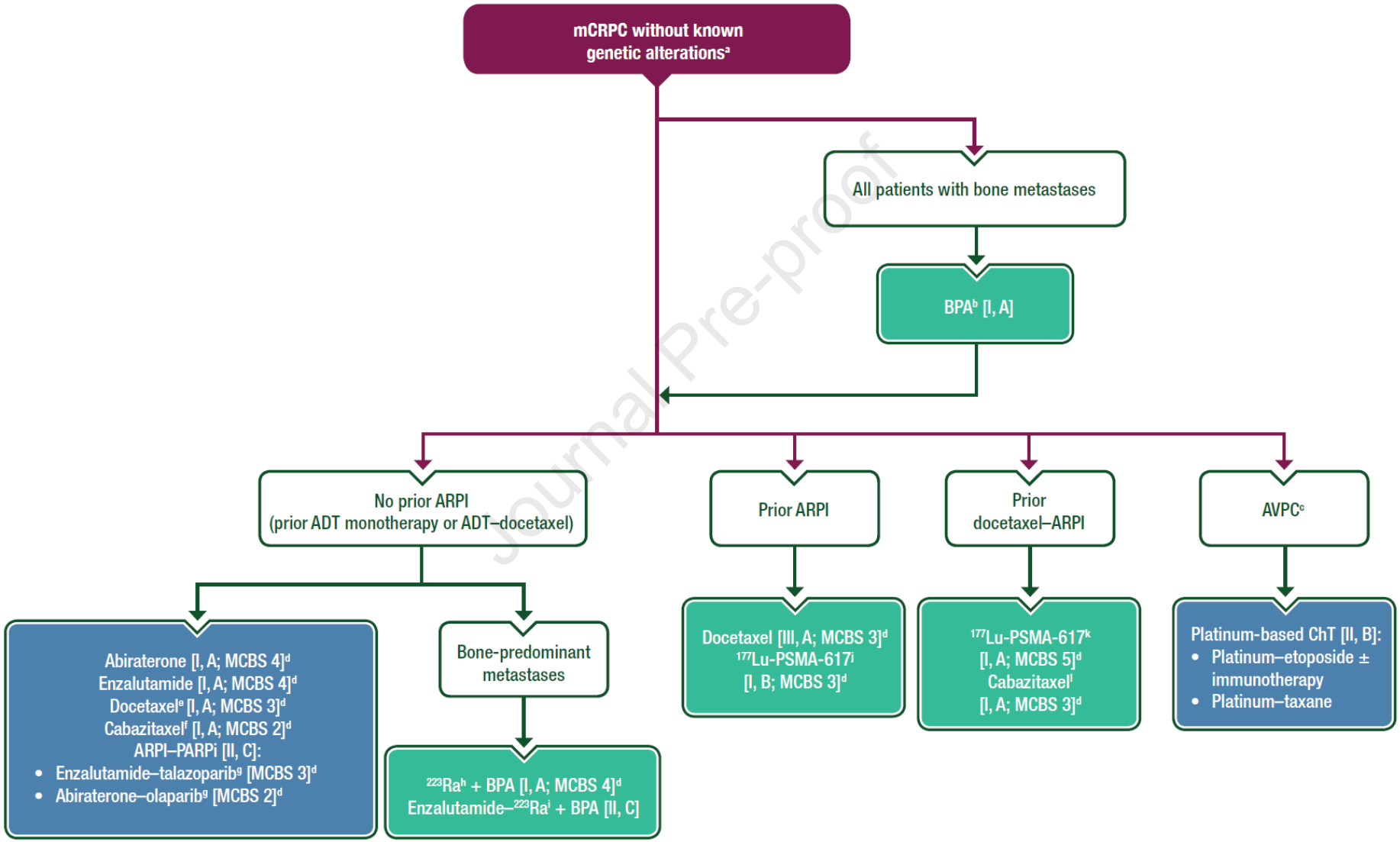
Purple: algorithm title; blue: systemic anticancer therapy or their combination.

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.

[a]PSA doubling time <10 months and estimated life expectancy >5 years.

[b]ESMO-MCBS v2.0[100] 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).

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.

^{177}Lu-PSMA-617, lutetium-177 PSMA-617; ^{223}Ra, 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.

[a]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].

[b]BPAs are administered concomitantly with anticancer treatments.

[c]A 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].

[d]ESMO-MCBS v2.0[100] 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).

[e]If no prior treatment with docetaxel and fit to receive docetaxel.

[f]If prior treatment with docetaxel and fit to receive cabazitaxel.

[g]EMA approved, not FDA approved in this setting.

[h]If prior treatment with docetaxel or unfit to receive it, and with no known visceral metastases.

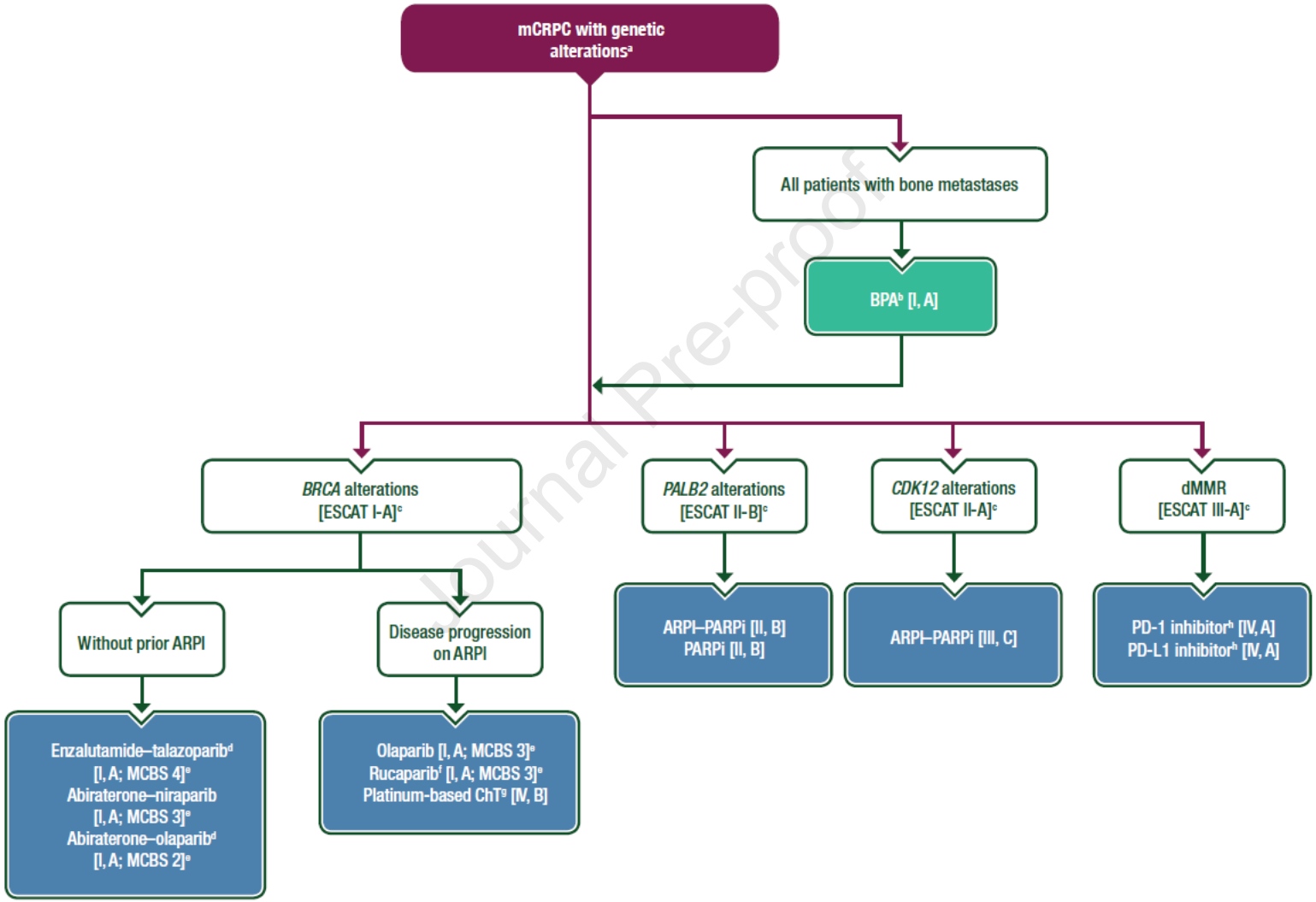
[i]Not EMA or FDA approved.

[j]In patients with PSMA-positive lesions who are not immediate candidates for docetaxel; FDA approved, not EMA approved.

[k]In patients with ≥1 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].

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

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.

[a]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]. 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].

[b]BPAs are administered concomitantly with anticancer treatments.

[c]ESCAT 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]

[d]FDA approved, not EMA approved in this setting.

[e]ESMO-MCBS v2.0[100] 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).

[f]FDA approved, not EMA approved.

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

[h]Treatment should begin as soon as possible during the course of disease.

DISCLOSURE

KF reports personal fees as an invited speaker from Cancerodigest, Clinical Care Options, Darman Strategik Numerik, eChinaHealth, ED MedResources, Epics, Health Podcast, Hopes, Medscape, Oseus, PeerVoice, Research to Practice, Tactics and Urotoday; personal fees for expert testimony from Access infinity, Arivan, Axiom, Globe Life Sciences, MD to Market, PSI and REACH Market Research; personal fees providing comments on new data from Cancer Expert Now; institutional fees for advisory board membership from Astellas, AstraZeneca, Bayer, Daiichi Sankyo, Janssen, MSD, Novartis/Advanced Accelerator Applications and Pfizer; institutional fees as an invited speaker from Astellas, AstraZeneca, Bayer, Janssen, MSD, Novartis and Pfizer; institutional research grants as a trial chair from AstraZeneca, Bayer, Bristol Myers Squibb (BMS), Janssen, MSD, Orion and Pfizer; institutional funding as coordinating principal investigator (PI) from Novartis; and non-remunerated activities as PI for AstraZeneca, Bayer, BMS, Clovis, Merck, Novartis/Advanced Accelerator Applications, Orion and Pfizer.

GA reports personal fees for advisory board membership from Astellas, AstraZeneca, Bayer, Blue Earth Therapeutics, BMS, Janssen, Merck, MSD, Novartis, Pfizer, Sanofi and Veracyte; personal fees as an invited speaker from Astellas, AstraZeneca, Janssen and Sanofi; personal royalties from Artera and the Institute of Cancer Research (was included in list of rewards to discoverers of abiraterone); personal travel expenses from Amgen, Merck Serono and Pfizer; institutional research grants from Astellas, Janssen and Novartis; institutional funding from Blue Earth Therapeutics and Veracyte; institutional funding as local PI from Novartis and Pfizer; institutional funding as coordinating PI from Janssen; institutional licencing fees from Veracyte; and a non-remunerated role as project lead for Artera and Veracyte.

AAA reports personal fees for advisory board membership from Amgen, Arvinas, Astellas, AstraZeneca, Bayer, BMS, Daiichii Sankyo, Ipsen, Janssen, Merck Serono, MSD, Novartis, Noxopharm, Pfizer, Sanofi, Telix and Tolmar; personal fees as an invited speaker from Amgen, Astellas, Bayer, BMS, Ipsen, Janssen, Merck Serono and

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GB reports personal fees for advisory board membership from Astellas; and personal fees as an invited speaker from Astellas.

HB reports personal fees for advisory board membership from Amgen, AstraZeneca, Daiichi Sankyo, Janssen, Merck, Novartis, Pfizer and Sanofi; institutional research grants from Circle Pharma, Daiichi Sankyo and Novartis; and institutional funding from BMS.

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FB reports no potential conflicts of interest.

ECa reports personal fees for advisory board membership from AstraZeneca, Bayer, Daiichi Sankyo, Janssen, Lilly, Medscape, MSD, Novartis and Pfizer; personal fees as an invited speaker from Astellas, AstraZeneca, Janssen, PeerVoice and Pfizer; personal fees for a writing engagement from Pfizer; personal fees as a steering committee member from Janssen, Merck Serono, Pfizer and Telix; institutional research grants from Bayer, Janssen and Pfizer; and institutional funding as local PI from AstraZeneca, Janssen, Macrogenics, MSD and Pfizer.

ECo reports personal fees as an invited speaker from Janssen, and a non-remunerated advisory role as a consulting pathologist for EAU Guidelines.

JdB reports personal fees for advisory board membership from Amgen, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Boehringer Ingelheim, CellCentric, Crescendo, Daiichi Sankyo, Eisai, Genentech/Roche, Genmab, GSK, ImCheck Therapeutics, Janssen, Menarini Silicon Biosystems, Merck Serono, MSD, MetaCurUm, Myricx, Nurix Therapeutics, Oncternal Therapeutics, Orion Pharma, Pfizer, QIAGEN, Sanofi Aventis, Sierra Oncology, Taiho Pharmaceuticals, Terumo and Vertex Pharmaceuticals; personal fees for a writing engagement from AstraZeneca, Bayer, Daiichi Sankyo, Genentech/Roche, GSK, Harpoon, Merck Serono, Pfizer, Sanofi Aventis, Sierra Oncology; institutional fees for advisory board membership from Dark

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AD reports a non-remunerated advisory role for Europa Uomo.

EE reports personal fees for advisory board membership from Astellas, AstraZeneca, Bayer, Janssen and Merck; and institutional funding as coordinating PI from Janssen and Sanofi.

LE reports personal fees for advisory board membership from Clarity Pharma and Novartis; personal fees as an invited speaker from AstraZeneca and GE HealthCare; institutional fees as an invited speaker from Astellas; institutional research grant from Novartis; and institutional funding as coordinating PI from Clarity Pharma and Telix.

SF reports personal fees for advisory board membership from Immedica, Novartis/Advanced Accelerator Applications, Sofie and Telix; personal fees as an invited speaker from Advanced Accelerator Applications, Astellas, Bayer, Blue Earth Therapeutics, GE HealthCare, Novartis, Sanofi and United Imaging; and personal fees for personnel training from Bayer.

VF reports institutional fees as an invited speaker for Astellas, Janssen, MSD and Novartis; and institutional funding as local PI from Janssen.

AGdA reports personal fees for advisory board membership from Advanced Accelerator Applications, AstraZeneca, Bayer, BMS, Eisai, EUSA Pharma, Janssen, MSD, Novartis, Pfizer and Veracyte; personal fees as an invited speaker from Astellas, Casen Recordati, Ipsen, Merck and Pfizer; personal fees for a writing engagement from Bayer; personal fees for expert testimony from Roche; an institutional research grant from

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GG reports personal travel expenses from Amgen, AstraZeneca, Bayer, BMS, MSD and Novartis/Advanced Accelerator Applications; institutional fees for advisory board membership from Astellas, AstraZeneca, Bayer, BMS, Curium, Eisai, Gilead, Ipsen, Janssen and Pfizer; and institutional fees as an invited speaker from Amgen, AstraZeneca, Bayer, BMS, Ipsen, Janssen, MSD and Novartis/Advanced Accelerator Applications.

NDJ reports personal fees for advisory board membership from AstraZeneca (PARP inhibitors), Bayer (novel hormone therapies for prostate cancer), Clovis (prostate cancer therapies), Janssen (prostate cancer therapies), Merck (bladder cancer therapy), Novartis (prostate cancer therapies) and Sanofi (docetaxel); personal fees as an invited speaker from MSD UK (lectures on therapy for advanced prostate cancer in Brazil, August 2022) and Novartis (^{177}Lu-PSMA-617 at conference in Sao Paulo); institutional fees for expert testimony from Janssen (submission support regarding licensing for abiraterone) and Sanofi (providing STAMPEDE trial data to facilitate licence extensions internationally for docetaxel); and institutional funding as coordinating PI from Astellas (STAMPEDE trial), AstraZeneca (RAD-IO trial in bladder cancer), Janssen (STAMPEDE trial) and Novartis (^{177}Lu-PSMA-617 comparison in STAMPEDE2 trial).

RK reports institutional advisory board membership from Amgen, AstraZeneca, Bayer, BMS, Ferring, Ipsen, Johnson & Johnson, MSD and Pfizer; institutional fees as an invited speaker from Amgen, Astellas, AstraZeneca, BMS, Ipsen, Johnson & Johnson, Merck, MSD, Novartis and Sanofi; institutional research grants from Eisai, Johnson & Johnson and Sanofi; and non-remunerated leadership roles for the International Kidney Cancer Coalition, Singapore Society of Oncology (past President), Singapore Cancer

Society (Vice Chairman) and the International Society of Geriatric Oncology (past President).

RSM reports personal fees for advisory board membership from Amgen, Bayer, BMS, Janssen and Pfizer; personal fees as an invited speaker from Astellas, Ipsen, Merck Serono and MSD; institutional fees as local PI for Astellas, Bayer, BMS and Regeneron; and institutional fees as coordinating PI for MSD.

NM reports personal fees for advisory board membership from Astellas, AstraZeneca, Johnson & Johnson, MSD and Pfizer; personal fees as an invited speaker from Ismar Healthcare and Medscape; personal funding from Janssen; institutional fees for advisory board membership from Bayer and Janssen; institutional fees as an invited speaker from Johnson & Johnson, Bureau Prevents and Travel Congress Management B.V.; institutional research grant from AstraZeneca, BMS and EUROSTAR; institutional funding from Astellas, Janssen and Pfizer; institutional fees as coordinating PI from BMS and Janssen; non-remunerated PI for the Prospective Bladder Cancer Infrastructure (Netherlands); and non-remunerated roles as member of the ESMO Faculty (GU, Prostate) and member of the ESMO Publishing Working Group (2014-2023).

CP reports personal fees for Independent Data Monitoring Committee (IDMC) membership from Telix; and institutional fees for advisory board membership from Janssen and Novartis.

RMR-P reports personal fees as an invited speaker from Bayer, Bracco, Ipsen and Janssen; and personal fees for expert testimony from Incepto.

MAR reports personal fees for scientific advisory board membership from NeoGenomics; personal stocks/shares in Owkin and Verintas Therapeutics; a non-renumerated role as PI for a research project supported by Roche; and a non-remunerated research collaboration with Genentech.

FS reports personal fees for advisory board membership from Astellas, AstraZeneca, Bayer, BMS, Janssen, Merck, Novartis, Pfizer and Sumitomo; institutional fees as local

PI for Astellas, Bayer, BMS, Janssen, Merck, Novartis, Pfizer and Sanofi; institutional fees as coordinating PI for AstraZeneca; and non-remunerated roles as PI for AbbVie, AstraZeneca, Bayer and Novartis.

CS reports personal fees for advisory board membership from AdvanCell, Astellas, Bayer, BMS, Genentech/Roche and Pfizer; personal fees for consultancy from AdvanCell, Amgen, Astellas, Bayer, Genentech/Roche, Janssen, Novartis and Pfizer; personal stocks/shares from AdvanCell and Perthera; institutional licensing fees from Exelixis; and institutional research grants from Astellas, Bayer, Dendreon, Janssen, Pfizer and Sanofi.

DT reports personal fees for advisory board membership from A3P Biomedical, Astellas, AstraZeneca, Bayer, Novartis, Pfizer, Roche and Veracyte; personal fees as an invited speaker from Amgen, Apogepha, Ipsen, Janssen and Takeda; and an institutional research grant from Janssen.

BT reports personal fees for advisory board membership from Amgen, Astellas, AstraZeneca, Bayer, Janssen, MSD, Myovant, Novartis, Pfizer and Sanofi; personal fees as an invited speaker from Accord, Amgen, Astellas and Ferring; personal fees for expert testimony from Astellas; a non-remunerated role as past president of the Board of Directors for the European Organisation of Research and Treatment of Cancer (EORTC); and a non-remunerated role as member of the Board of Directors for the International Society for the Study and Exchange of Evidence from Clinical Research and Medical Experience.

ACT reports personal fees as an invited speaker from Astellas, Bayer, Elekta and Janssen; personal fees for role as GU Editor of the *International Journal of Radiation Oncology Biology Physics* (*IJROBP*); institutional fees as an invited speaker from Accuray; institutional research grants from Accuray, Artera, Elekta and Varian; institutional fees as consortium steering committee chair for Elekta; non-remunerated role as an editorial team leader for *IJROBP*; non-remunerated advisory role for the Prostate Cancer UK Clinical Advisory Committee; and non-remunerated member of the

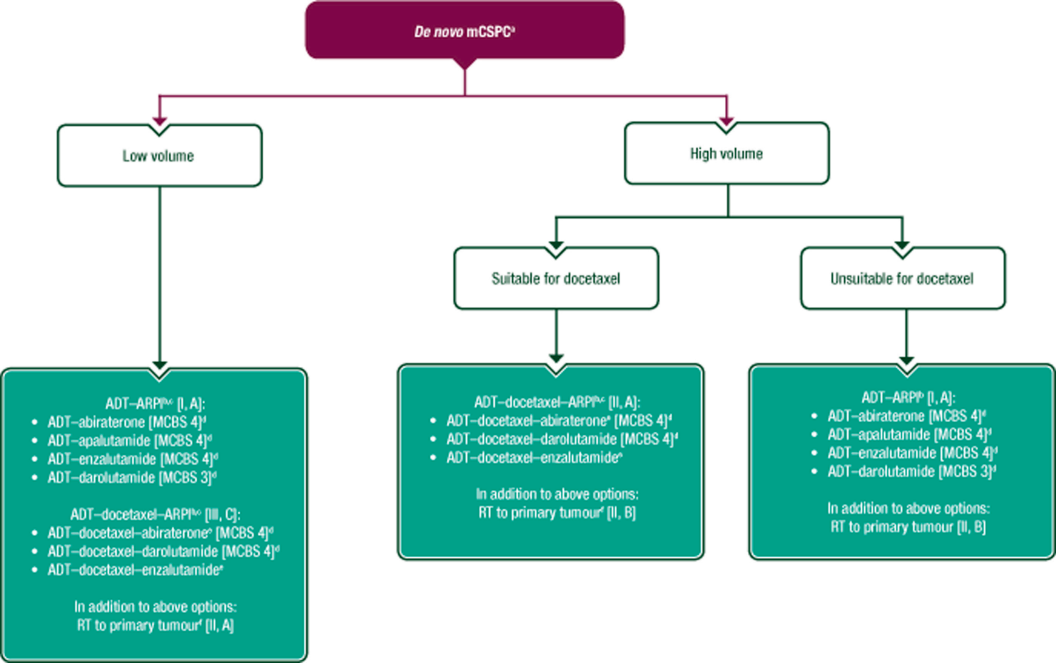
American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology (ESTRO).

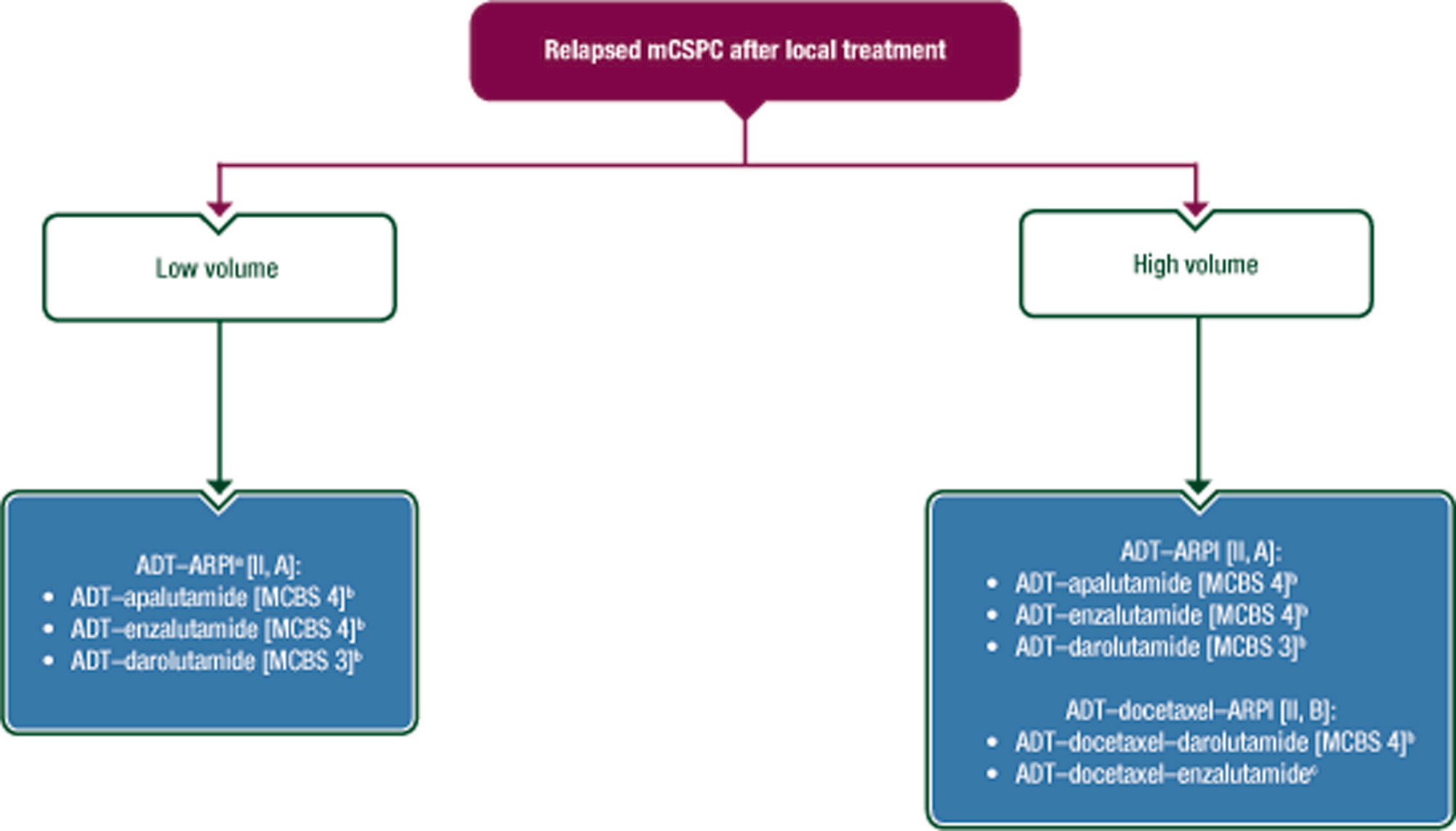
JW reports institutional fees for advisory board membership from Janssen and Telix; institutional fees as an invited speaker from Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Curium, Intuitive, Ipsen, Janssen and Novartis; institutional funding for expert testimony from Intuitive; other institutional funding from Exact Imaging and Janssen; and a non-remunerated leadership role for the EAU.

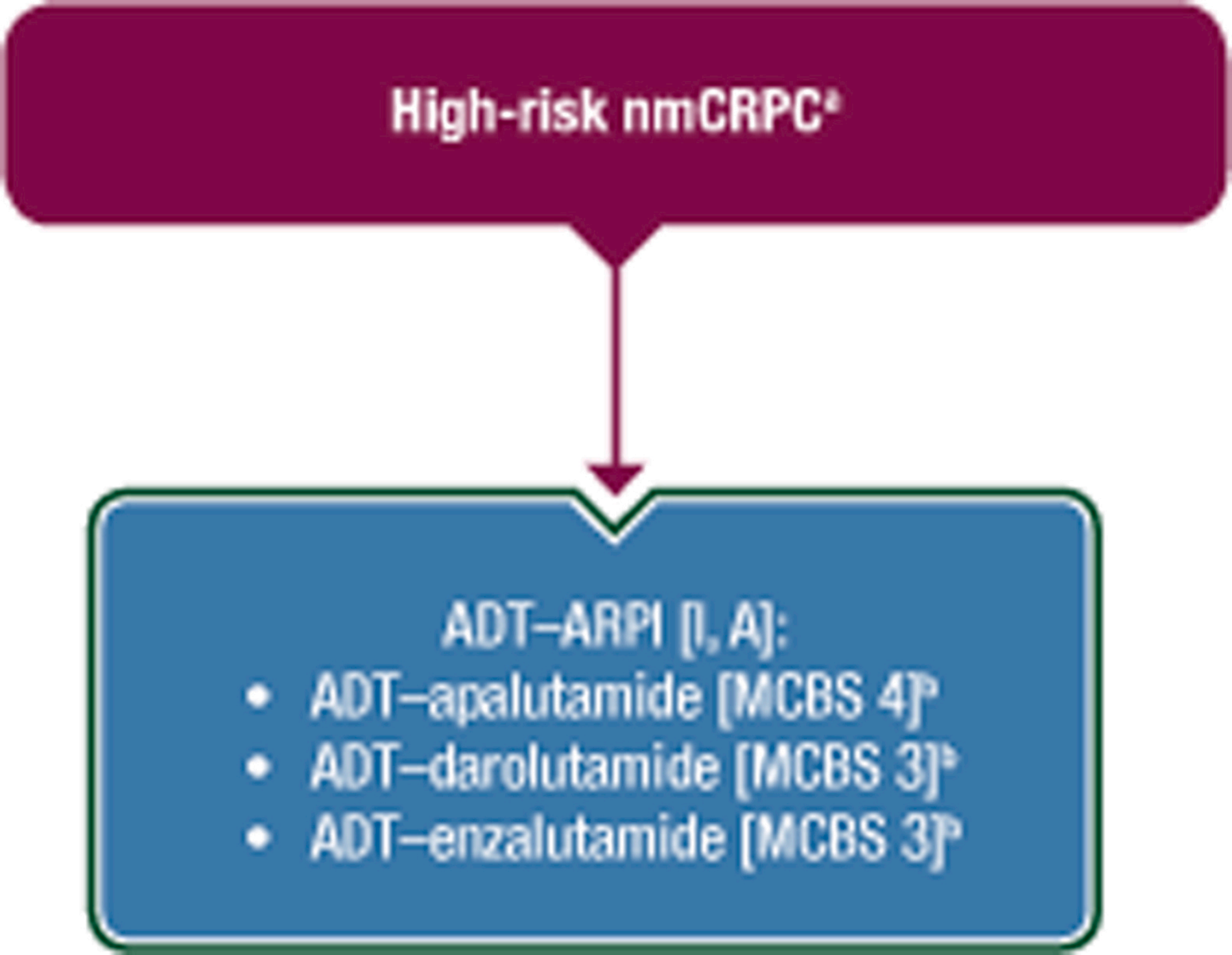
TZ reports personal fees as an invited speaker from EAU, European Multidisciplinary Congress on Urological Cancers (EMUC) and ESMO; personal travel expenses from Ferring; institutional fees for advisory board membership from Accord and Astellas; institutional fees as an invited speaker from Abbott, Debiopharm, Janssen, Silvio Grasso Consulting, Swiss Cancer Institute; institutional research grants from Debiopharm and Varian; non-remunerated advisory role as ESTRO representative for the EMUC; non-remunerated leadership role as Chair of the Guidelines Committee for ESTRO; non-remunerated role as member of the Board of Directors for Fond'Action, Groupe Francophone Radiothérapie Urologique and the International Stereotactic Radiosurgery Society (ISRS); non-remunerated member of the scientific board for Swiss Cancer Institute; and non-remunerated membership of EORTC, ESMO, ESTRO, ISRS and the Scientific Association of Swiss Radiation Oncology.

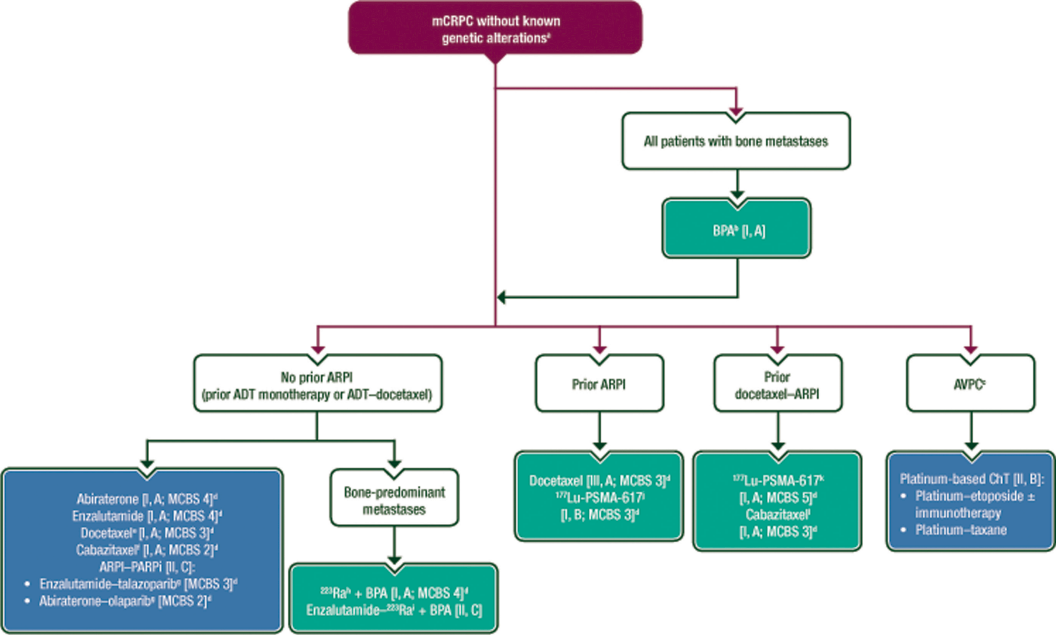
SG reports personal fees for advisory board membership from the University of Applied Sciences and Arts of Southern Switzerland; personal fees as an invited speaker for ESMO and Meister ConCept GmbH; personal travel grants from Bayer, Gilead, Johnson & Johnson and Intellisphere LLC; a patent for a biomarker of Proteomedix/Onconetix; institutional fees for advisory board membership from Amgen, Astellas, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, GSK, Innomedica, Ipsen, LinkinVax, Macrogenics, Merck, MSD, Novartis and Pfizer; institutional fees as an invited speaker for AdMeTech Foundation, ASCO GU, EPG Health, ESMO, Intellisphere LLC, Medtoday Switzerland, Meister ConCept GmbH, OriKata, Swiss Group for Clinical Cancer Research, Silvio Grasso Consulting and UroPrática Group in São Paulo;

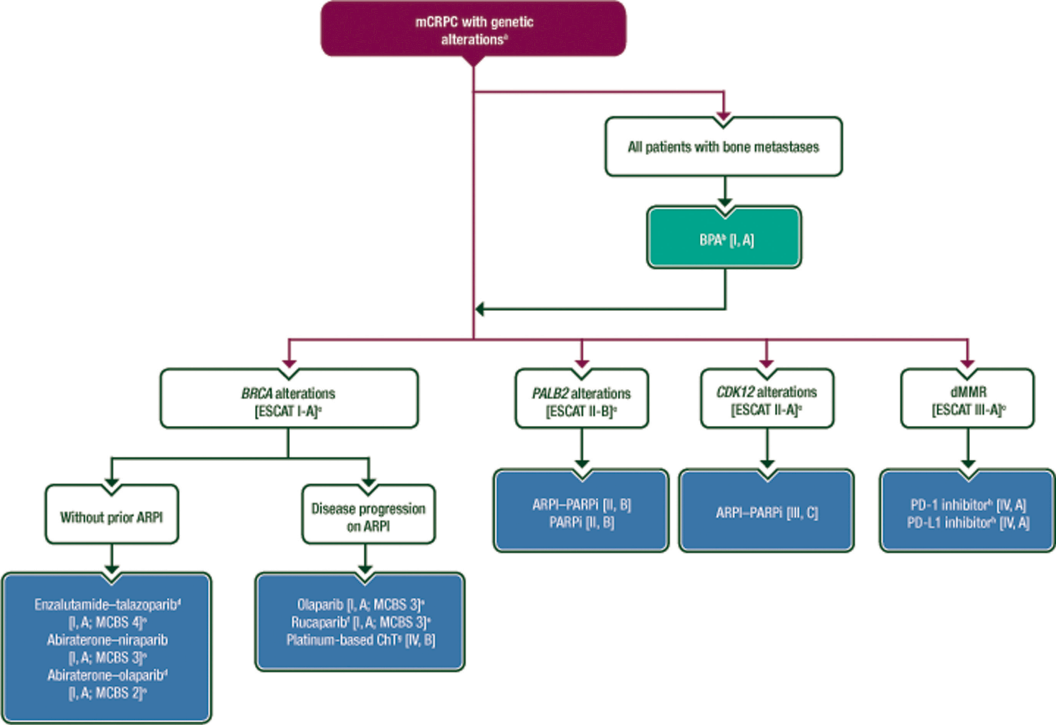
institutional funding as a co-investigator from Astellas; other institutional fees from Avalere Health (expert testimony), BMS (consultancy), PeerVoice (interview), Pfizer (Scientific Committee Pfizer Forschungspreis) and WebMD-Medscape (faculty activity); non-remunerated advisory roles for Pfizer, ProteoMediX and Unicancer; and other non-remunerated activities for ASCO (guest engagement agreement) and AstraZeneca (senior executive meeting).


De novo mCSPC[a]
Low volume
High volume
Suitable for docetaxel
Unsuitable for docetaxel
ADT–ARPI[b,c] [I, A]:
• ADT–abiraterone [MCBS 4][d]
• ADT–apalutamide [MCBS 4][d]
• ADT–enzalutamide [MCBS 4][d]
• ADT–darolutamide [MCBS 3][d]
ADT–docetaxel–ARPI[b,c] [III, C]:
• ADT–docetaxel–abiraterone[e] [MCBS 4][d]
• ADT–docetaxel–darolutamide [MCBS 4][d]
• ADT–docetaxel–enzalutamide[e]
In addition to above options:
RT to primary tumour[f] [II, A]
ADT–docetaxel–ARPI[b,c] [II, A]:
• ADT–docetaxel–abiraterone[e] [MCBS 4][d]
• ADT–docetaxel–darolutamide [MCBS 4][d]
• ADT–docetaxel–enzalutamide[e]
In addition to above options:
RT to primary tumour[f] [II, B]
ADT–ARPI[b] [I, A]:
• ADT–abiraterone [MCBS 4][d]
• ADT–apalutamide [MCBS 4][d]
• ADT–enzalutamide [MCBS 4][d]
• ADT–darolutamide [MCBS 3][d]
In addition to above options:
RT to primary tumour [II, B]


Relapsed mCSPC after local treatment
Low volume
High volume
ADT–ARPI[a] [II, A]:
• ADT–apalutamide [MCBS 4][b]
• ADT–enzalutamide [MCBS 4][b]
• ADT–darolutamide [MCBS 3][b]
ADT–ARPI [II, A]:
• ADT–apalutamide [MCBS 4][b]
• ADT–enzalutamide [MCBS 4][b]
• ADT–darolutamide [MCBS 3][b]
ADT–docetaxel–ARPI [II, B]:
• ADT–docetaxel–darolutamide [MCBS 4][b]
• ADT–docetaxel–enzalutamide[c]


High-risk nmCRPC[a]
ADT–ARPI [I, A]:
• ADT–apalutamide [MCBS 4][b]
• ADT–darolutamide [MCBS 3][b]
• ADT–enzalutamide [MCBS 3][b]


mCRPC without known genetic alterations[a]
All patients with bone metastases
BPA[b] [I, A]
No prior ARPI (prior ADT monotherapy or ADT–docetaxel)
Prior ARPI
Prior docetaxel–ARPI
AVPC[c]
Abiraterone [I, A; MCBS 4][d]
Enzalutamide [I, A; MCBS 4][d]
Docetaxel[e] [I, A; MCBS 3][d]
Cabazitaxel[f] [I, A; MCBS 2][d]
ARPI–PARPi [II, C]:
• Enzalutamide–talazoparib[g] [MCBS 3][d]
• Abiraterone–olaparib[g] [MCBS 2][d]
Bone-predominant metastases
223Ra[h] + BPA [I, A; MCBS 4][d]
Enzalutamide–223Ra[i] + BPA [II, C]
Docetaxel [III, A; MCBS 3][d]
177Lu-PSMA-617[j] [I, B; MCBS 3][d]
177Lu-PSMA-617[k] [I, A; MCBS 5][d]
Cabazitaxel[f] [I, A; MCBS 3][d]
Platinum-based ChT [II, B]:
• Platinum–etoposide ± immunotherapy
• Platinum–taxane


mCRPC with genetic alterations[a]
All patients with bone metastases
BPA[b] [I, A]
BRCA alterations [ESCAT I-A][a]
PALB2 alterations [ESCAT II-B][a]
CDK12 alterations [ESCAT II-A][a]
dMMR [ESCAT III-A][c]
Without prior ARPI
Disease progression on ARPI
ARPI–PARPi [II, B]
PARPi [II, B]
ARPI–PARPi [III, C]
PD-1 inhibitor[b] [IV, A]
PD-L1 inhibitor[b] [IV, A]
Enzalutamide–talazoparib[d] [I, A; MCBS 4][e]
Abiraterone–niraparib [I, A; MCBS 3][e]
Abiraterone–olaparib[d] [I, A; MCBS 2][e]
Olaparib [I, A; MCBS 3][e]
Rucaparib[f] [I, A; MCBS 3][e]
Platinum-based ChT[g] [IV, B]