ORIGINAL RESEARCH

Bone health and body composition in prostate cancer: Meet-URO and AIOM consensus about prevention and management strategies

M. C. Cursano[1†], A. A. Valsecchi[2†], F. Pantano[3], M. Di Maio[2], G. Procopio[4], A. Berruti[5], F. Bertoldo[6], M. Tucci[7], U. De Giorgi[1‡] & D. Santini[8*‡], on behalf of the Meet-URO and AIOM experts[§]

[1]Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola; [2]Department of Oncology, University of Turin, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Molinette, Turin; [3]Department of Medical Oncology, Campus Bio-Medico University, Rome; [4]Programma Prostata Fondazione Istituto Nazionale Tumori Milano, Milan; [5]Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia and ASST SpedaliCivili di Brescia, Brescia; [6]Emergency Medicine, Department of Medicine, University of Verona, Verona; [7]Department of Medical Oncology, Cardinal Massaia Hospital, Asti; [8]Oncologia Medica A, Policlinico Umberto 1, La Sapienza Università Di Roma, Rome, Italy

Available online 19 June 2024

Background: Prostate cancer (PCa) treatments are associated with a detrimental impact on bone health (BH) and body composition. However, the evidence on these issues is limited and contradictory. This consensus, based on the Delphi method, provides further guidance on BH management in PCa.

Materials and methods: In May 2023, a survey made up of 37 questions and 74 statements was developed by a group of oncologists and endocrinologists with expertise in PCa and BH. In June 2023, 67 selected Italian experts, belonging to the Italian scientific societies Italian Association of Medical Oncology and Italian Network for Research in Urologic-Oncology (Meet-URO), were invited by e-mail to complete it, rating their strength of agreement with each statement on a 5-point scale. An agreement ≥75% defined the statement as accepted.

Results: In non-metastatic hormone-sensitive PCa, the panel agreed that androgen deprivation therapy (ADT) alone implies sufficient fracture risk to warrant antifracture therapy with bone-targeting agents (BTAs) for cancer treatment-induced bone loss (CTIBL) prevention (79%). Therefore, no consensus was reached (48%) for the treatment with BTAs of patients receiving short-term ADT (<6 months). All patients receiving active treatment for metastatic hormone-sensitive PCa (75%), non-metastatic castration-resistant PCa (89%) and metastatic castration-resistant PCa (mCRPC) without bone metastases (84%) should be treated with BTAs at the doses and schedule for CTIBL prevention. All mCRPC patients with bone metastasis should be treated with BTAs to reduce skeletal-related events (94%). In all settings, the panel analyzed the type and timing of treatments and examinations to carry out for BH monitoring. The panel agreed on the higher risk of sarcopenic obesity of these patients and its correlation with bone fragility.

Conclusions: This consensus highlights areas lacking major agreement, like non-metastatic hormone-sensitive prostate cancer patients undergoing short-term ADT. Evaluation of these issues in prospective clinical trials and identification of early biomarkers of bone loss are particularly urgent.

Key words: bone health, body composition, prostate cancer, consensus, Meet-URO, AIOM

INTRODUCTION

Prostate cancer (PCa) is the most frequent cancer in men and represents the third leading cause of death.[1] However,

Correspondence to: Prof. Daniele Santini, Oncologia Medica A, Policlinico Umberto 1, La Sapienza Università Di RomaViale del Policlinico 155, 00161 Roma (RM), Italy. Tel: 003906 49971
E-mail: daniele.santini@uniroma1.it (D. Santini).

[†]These authors equally contributed to this work.
[‡]These authors are co-last authors.

survival is improving (5-year survival rate of 92% and a 10-year survival rate of 90%) as a result of new treatment strategies. For many years, androgen deprivation therapy (ADT) has been the standard of care for patients needing systemic therapy; to date, the combination of new hormone therapies (NHT), radioligand, poly-(ADP-ribose) polymerase (PARP) inhibitors and chemotherapy has been shown to be more effective in the management of PCa, both in the hormone sensitivity phase and in the castration-resistant disease.

Despite benefits associated with ADT, NHT and chemotherapy, these treatments cause several side-effects, including detrimental effects on bone health (BH).[2-5] As

the life expectancy of these patients increases, as well as age-related bone quality changes and possible comorbidities, the likelihood of presenting adverse events affecting BH increases.

Furthermore, PCa cells have a high bone tropism, which is responsible for the skeletal involvement observed in up to 90% of the cases in the advanced setting of PCa.[6] Preserving BH in PCa has to be a goal throughout the course of the disease.[7]

BH impairment has a detrimental effect on the individual's quality of life (QoL) and health status and imposes a considerable burden on health care resources.[8] Osteoporotic fractures increase the risk of death.

Furthermore, besides the quantitative and qualitative alterations of bone that increase the fracture risk, androgen deprivation is associated with increased fat body mass and decreased lean body mass, and these changes in body composition impair BH by increasing osteoporotic fractures and falls.[9,10]

There is a link between obesity and cancer progression.[11] Age-related immune deterioration is exacerbated by obesity and may impact on the metabolic landscape of tumor microenvironment, a unique metabolic niche, containing tumor, immune and stromal cells. Moreover, peritumoral adipose tissue is involved in tumor initiation, growth and invasion[12,13] and may promote therapeutic resistance.[14] Obesity may affect BH through the so-called obesity paradox: in obese people the negative effect of adiposity on BH is blunted by their higher estrogen levels (due to enhanced aromatase activity) that increase bone mineral density (BMD). This phenomenon is lost in obese men on ADT, who may be at higher risk of bone fractures; in these men, ADT-related loss of bone protection associated with estrogens is added to the detrimental changes in bone quality associated with adiposity.[8,15]

For this reason, the present paper focuses not only on BH and its ongoing qualitative and quantitative changes during PCa treatments, but also on body composition changes.

Despite the importance of this issue, the level of evidence of these topics in PCa is limited and conflicting.

The aim of this project is to gain insights from a multidisciplinary group of experts (oncologists with expertise in genitourinary tumors and endocrinologist) in order to provide further guidance on clinically relevant topics in BH management of patients with PCa.

Firstly, the available evidence on BH during novel treatment strategies (ADT, NHTs and chemotherapy) and bone turnover inhibitors on the bone was reviewed for each setting of PCa disease [non-metastatic hormone-sensitive prostate cancer (nmHSPC), metastatic hormone-sensitive prostate cancer (mHSPC), non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-resistant prostate cancer (mCRPC)].

Then, several questions were identified on specific topics for each disease setting; for each question, statements were formulated to which the panel of Italian experts were asked to express their consent or dissent.

The goal of this work is to complement existing guidelines and optimize the monitoring and treatment of BH in PCa.

MATERIALS AND METHODS

In May 2023, DS and UDG, two oncologists, planned this collaboration between the Italian Network for Research in Urologic-Oncology (Meet-URO) and the Italian Association of Medical Oncology (AIOM), focused on the management of BH and body composition in patients with PCa, using the Delphi survey and consensus approach.

They brought together a group of six experts, including five oncologists (MCC, FP, AB, MDM, AAV) and one endocrinologist (FB), to establish a project steering committee.

MCC and FP collaboratively developed a set of questions and statements on diagnostic and therapeutic strategies for management of BH and body composition in patients with PCa based on a systematic literature review, focusing on topics for which there was no high-quality evidence or for which available recommendations were conflicting. Then DS, UDG, AB and FB reviewed and discussed the survey, based on their expertise. MDM and AAV dealt with the methodological part of the consensus and the analysis of the results.

The survey was made up of 37 questions and 74 statements, in the English language, divided into four groups corresponding to the four settings of prostate disease: nmHSPC (11 questions and 28 statements); mHSPC (7 questions and 11 statements); nmCRPC (8 questions and 14 statements); mCRPC (11 questions and 21 statements). Descriptive analyses are detailed in the results section and all detailed answers are summarized in Tables 1-4.

In June 2023, an invitation to complete the survey was sent by e-mail to 67 selected experts in BH and urological cancers, members of Meet-URO and/or AIOM. Consent to participate was implied by registering and completing the online questionnaire. The answers to the questions were provided on a voluntary basis and all replies were anonymized in accordance with national and EU rules on the protection of the processing of personal and sensitive data (European Regulation n.679/2016, c.d. GDPR, and Italian legislation on Privacy).

All health care professionals were asked to rate their strength of agreement with each statement on a 5-point scale: strongly disagree, disagree, uncertain, agree and strongly agree. They had to vote to all statements in order to be able to submit the survey. Participants were also encouraged to suggest any changes to the statement in case of disagreement in a free space for comments. These were then reviewed by the project steering committee in order to decide whether statements that did not reach a

Table 1. Non-metastatic hormone-sensitive prostate cancer

Question	Statement	Level of consensus		
		Agree (%)	Disagree (%)	Uncertain (%)
1. Among patients receiving ADT, which are those at risk of fracture?[9,16]	1.1 Adjuvant hormone therapy alone implies sufficient fracture risk to warrant antifracture therapy as primary or secondary prevention, independently of the presence of other fracture risk factors.	79.4	11.1	9.5
	1.2 All patients receiving short-term ADT (3-6 months) should be treated with antifracture prevention therapy.	48	37	15
	1.3 All patients receiving long-term ADT (>6 months) should be treated with antifracture prevention therapy.	88	2	10
2. When should antiresorptive therapy be started in patients with PCa starting hormone therapy?[17]	2.1 BTAs should be considered immediately from the start of hormonal therapy itself.	80	8.3	11.7
3. In males affected by PCa on ADT, which are the drugs to be used for the reduction of the risk of fracture?[18,19]	3.1 In patients with PCa on ADT for the prevention of risk of fracture denosumab 60 mg every 6 months is advisable. In case of prescriptive ineligibility to therapy with denosumab and/or lack of reimbursement, the choice of another BTA (alendronate 70 mg weekly, risedronate 35 mg weekly or zoledronic acid 4 mg every 6 months) might be a choice.	93.7	0	6.3
4. Are vitamin D and calcium supplementations alone sufficient to maintain bone health or prevent fragility fractures in patients with PCa starting hormone therapy?[20]	4.1 Vitamin D and calcium supplementation alone are not sufficient to maintain bone health and to prevent fragility fractures.[20]	76.7	5	18.3
	4.2 Before starting and during any hormonal therapy, the levels of vitamin D ($\geq$30 ng/ml) should be evaluated and normalized, regardless of the bone-modifying agent.	91.7	1.6	6.7
	4.3 The administration of calcium and daily dose of vitamin D 1500-2000 IU, to reach and maintain the value of 30 ng/ml (75 nmol/l), during antiresorptive therapy is mandatory.	93.3	0	6.7
5. Is intermittent ADT useful for maintaining bone health?[21]	5.1 The use of intermittent ADT does not yield a reduction in bone events (osteoporosis or fracture) and use of BTAs should be considered even in patients receiving intermittent ADT.	85.7	8	6.3
6. How to diagnose and monitor the bone health in nmHSPC during and after ADT?[22]	6.1 To monitor bone health during ADT, the following assessments should be carried out at baseline and every 12-18 months thereafter: Vitamin D, serum calcium and PTH.	81.7	5	13.3
	6.2 To monitor bone health during ADT, the following assessments might be carried out, if possible, at baseline and every 18 months thereafter: DEXA scan (for BMD) and, if available, vertebral morphometry.	95.2	0	4.8
	6.3 To monitor bone health during ADT, the following assessments might be carried out, if possible, at baseline and every 18 months thereafter: DEXA scan with TBS.	92.1	1.6	6.3
	6.4 To monitor bone health during ADT, the following assessments should be carried out at baseline and every 12-18 months thereafter: Bone turnover markers, height, weight and BMI and body composition (by DEXA, bioelectrical impedance or plicometry) besides body mass index.	76.7	3.3	20
	6.5 Given the high prevalence of risk factors for fractures independent of hormone therapy and the high prevalence of vertebral fractures already present at the time of cancer diagnosis, all subjects with PCa should be investigated for the presence of fragility fractures by traditional radiography at baseline.	60	15	25
	6.6 Patients with nmHSPC receiving ADT may benefit from a supervised physical activity program in terms of bone health regardless of whether they are receiving antiresorptive therapy or not.	98.3	0	1.7
7. In nmHSPC patients treated with antiresorptive drugs (BPs and denosumab) for bone health, is an oral cavity assessment recommended before starting therapy, to reduce the risk of subsequent MRONJ?[23]	7.1 Before starting treatment with BPs or denosumab, adequately informed patients have to carry out a dental visit to evaluate their oral health, to set up an adequate prevention program and possibly treat local pathologies.	85	8.3	6.7

Continued

Table 1. Continued

Question	Statement	Level of consensus		
		Agree (%)	Disagree (%)	Uncertain (%)
8. How to manage any dental procedures that may be necessary during antiresorptive treatments for bone health in nmHSPC?	8.1 In patients on treatment with BPs, their long half-life leads to an inhibition effect on osteoclastic function of unpredictable duration over time, even after a single administration. A temporary suspension of BPs (at least 7 days before and at least 6-8 weeks after the surgical procedure) could reduce their anti-angiogenic effect on the soft tissues, in order to therefore favor the vascularization of the healing tissues. The resumption of pharmacological therapy will be possible 6-8 weeks after the dental surgical procedure, once the post-surgical oral site has healed.	83.3	5	11.7
	8.2 In patients on treatment with denosumab, the urgency of the surgical procedure must first be assessed. In the presence of urgent invasive dental procedures, it is advisable to carry out the dental surgical maneuvers 3 weeks after the last administration of denosumab 60 mg and to apply *ad hoc* medical—surgical protocol. In the presence of invasive dental procedures that can be postponed, it is advisable to carry out the surgical maneuvers starting from the end of the fifth month after the last administration of denosumab. The resumption of pharmacological therapy will be possible 6-8 weeks after the dental surgical procedure, once the post-surgical oral site has healed.	91.7	0	8.3
9. Patients on adjuvant ADT: how long should be treated with BTAs for the prevention of the risk of fractures?	9.1 For patients on adjuvant ADT, therapy with antiresorptive drugs should be continued at least for the entire duration of the adjuvant hormone therapy itself. After the end of adjuvant ADT, the risk fracture of the patient should be reassessed to evaluate the possible continuation of antiresorptive therapy.	93.3	0	6.7
10. How to continue denosumab or BPs beyond the duration of adjuvant ADT? Is there maximum treatment duration and what to do after discontinuation?	10.1 In PCa patients on treatment with BPs or denosumab for CTIBL, after discontinuation of ADT, the fracture risk should be reassessed (using a validated algorithm for fracture risk, such as DeFRA, FRAX). If the patient experienced no fracture during treatment and has no other risk factors (BMD T-score > -2.5, obesity, age, sarcopenia, previous osteoporotic fractures, parent fractured hip, current smoking or alcohol, glucocorticoids, rheumatoid arthritis, secondary osteoporosis), BTAs can be discontinued, and bone health can continue to be monitored. If the patient presents any additional risk factor, monitoring and antiresorptive therapy with BPs or denosumab should be carried on.	85	1.7	13.3
	10.2 For patients who experienced fragility fracture or a decline in BMD during BPs, treatment could be switched to denosumab 60 mg 6 months.	75	0	25
	10.3 A decision to discontinue denosumab could be made after discontinuation of ADT, but bone turnover rebound and rapid bone loss must be monitored. Bisphosphonate (mainly zoledronic acid) therapy should be considered, especially in high-risk patients, according to prescriptive rules.	87.3	4.8	7.9
	10.4 Patients considered at high fracture risk could either continue denosumab therapy or be switched to BPs, in the absence of contraindications.	83.3	3.3	13.3
	10.5 For patients who discontinue denosumab and experience rapid bone loss or new fracture despite bisphosphonate administration, retreatment with denosumab is likely to stop fracture risk and restore BMD by reducing bone turnover.	61.7	0	38.3
	10.6 In patients who are not candidates for bisphosphonate therapy or who remain at high risk of fracture despite denosumab treatment, denosumab should be continued.	75	0	25
11. How to improve bone health in nmHSPC patients?[24,25]	11.1 All patients with nmHSPC should undergo a total body composition by DEXA, in addition to weight detection and BMI, for lean body mass and fat mass assessment at baseline and during androgen deprivation treatment to reduce cardiovascular risk and sarcopenic obesity risk and improve bone health.	81.7	3.3	15

Continued

Table 1. Continued				
Question	**Statement**	**Level of consensus**		
		Agree (%)	Disagree (%)	Uncertain (%)
	11.2 All patients with nmHSPC should undergo a nutritional assessment at baseline and during androgen deprivation treatment in order to reduce cardiovascular risk and sarcopenia risk and improve bone health.	85	8.3	6.7
	11.3 Supervised clinical exercise programs should be included in clinical care programs for nmHSPC.	93.3	0	6.7

ADT, androgen deprivation therapy; BMD, bone mineral density; BMI, body mass index; BPs, bisphosphonates; BTAs, bone-targeting agents; CTIBL, cancer treatment-induced bone loss; DEXA, dual-energy X-ray absorptiometry; MRONJ, medication-related osteonecrosis of the jaw; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PCa, prostate cancer; PTH, parathyroid hormone; TBS, trabecular bone score.

sufficient level of agreement should be changed in the next round.

Statements were evaluated as follows:
- If the agreement was ≥75% (defined as the percentage of 'agree' and 'strongly agree' on the total of respondents), the statement was accepted;
- If the agreement was >25% and <75%, the statement was not accepted and was eventually re-proposed in the subsequent round, modified based on participants' comments as described above;
- If the agreement was ≤25%, the statement was not accepted.

Three rounds of voting were conducted.

RESULTS

Preceding the MEET-URO BH consensus meeting, 37 questions and 74 statements were identified and sent to 67 panelists (MEET-URO and/or AIOM members and BH expert endocrinologists). Among them, 62 out of 67 (92.5%) members adhered to the consensus and 52 out of these 62 expressed their opinion on each single statement. Respondents' characteristics (affiliation, specialty and degree) are summarized in Supplementary Appendix A, available at https://doi.org/10.1016/j.esmoop.2024.103484.

In the nmHSPC setting, 11 questions and 28 statements were formulated; of these, 19 statements (68%) achieved an agreement >75% after the first vote and 1 statement (3.5%) was not accepted. The remaining eight statements (28.5%) were reworded based on the panelists' review and resubmitted for a second vote. Of these, seven were accepted after the second vote and one was rejected. On the basis of the panelists' observations, the latter was reworded and divided into two separate statements and resubmitted to the third vote: one statement was accepted and one was rejected (Table 1).

In the mHSPC setting, 7 questions and 11 statements were formulated; of these, 8 statements (73%) reached an agreement >75% after the first vote and 1 statement (9%) was rejected. The remaining two statements (18%) were reworded based on the panelists' review and resubmitted for a second vote and then accepted (Table 2).

In the nmCRPC setting, 8 questions and 14 statements were formulated; of these, 10 statements (71%) reached an

agreement >75% after the first vote and 1 statement (8%) was rejected. The remaining three statements (21%) were reworded based on the panelists' review and resubmitted for a second vote and then accepted (Table 3).

In the mCRPC setting, 11 questions and 21 statements were formulated; of these, 19 statements (90%) reached an agreement >75% after the first vote and the remaining 2 statements (10%) were reworded based on the panelists' review and resubmitted for a second vote and then accepted (Table 4).

In Supplementary Appendix B, available at https://doi.org/10.1016/j.esmoop.2024.103484, there is a summary of all the questions and statements and the existing literature for each setting.

DISCUSSION

Many patients with PCa may receive, according to the setting of disease, modern treatments which include ADT, radiation, NHT as well as chemotherapy. The goal of local and systemic treatment is to prolong survival and promote QoL. Since survival can be significantly prolonged by novel treatment options, long-term side-effects will become increasingly important to be recognized and adequately prevented and treated.

In the past, the intensification of treatment, through the use of ADT, NHT and chemotherapy, concerned patients with mCRPC; to date, treatment intensification has been shifted earlier in the non-metastatic and/or hormone-sensitive setting, leading to a consistent survival improvement but adding further considerations when balancing risk-to-benefit profiles.[38]

NHTs block systemic androgen action to a greater extent than conventional ADT; some studies investigated NHT effects on muscle, bone and fat. Abiraterone has been shown to cause a decrease in muscle mass, and, unexpectedly, also a decrease in visceral fat, the mechanism for which is uncertain.[39] Glucocorticoid co-administration, usually required to prevent abiraterone-associated mineralocorticoid excess, may compound adverse effects on body composition and bone mass. In addition, several trials have demonstrated that androgen deprivation increases fracture risk by over 30%, with an estimated number of harms of one fracture for every 30 patients treated.[40,41] Three years of treatment with enzalutamide is associated with an increase in fat body

Table 2. Metastatic hormone-sensitive prostate cancer

Question	Statement	Level of consensus		
		Agree (%)	Disagree (%)	Uncertain (%)
1. Among patients receiving systemic treatment for mHSPC, which are those at risk of fracture?[8]	1.1 All patients receiving ADT ± docetaxel ± NHT should be treated with bone-targeting agents for fragility fracture prevention.	75.4	8.2	16.4
2. Are there other independent fracture risk factors to consider when deciding to use drugs for bone health in patients with mHSPC?	2.1 In mHSPC the independent factors of fracture risk (BMD, familiarity with fragility fractures, corticosteroid therapy with >5 mg/prednisone equivalent in the past for >3 months consecutively or ongoing, metabolic bone diseases or fragilizing disease treatment, disability or high risk of fall, age, anamnesis for low-energy trauma fractures) should be evaluated before starting any antifracture prevention therapy. However, the fracture risk is independent of these factors that are, if present, additive in the risk estimation. Consequently, every patient candidate to treatment for mHSPC should receive bone-protective agents independently of the individual fracture risk.	78.7	9.8	11.5
3. When should antiresorptive therapy be initiated in males treated with systemic treatment for mHSPC?[26]	3.1 In mHSPC patients a therapy with antiresorptive drugs at the doses and schedule for SREs prevention should not be started.	80.3	4.9	14.8
4. In males in treatment for mHSPC, when should antiresorptive therapy be started and which drugs and schedules should be used for the prevention of CTIBL and the reduction of the risk of fracture?	4.1 BTAs should be considered from the start of ADT itself for primary prevention of CTIBL.	75.4	4.9	19.7
	4.2 In patients with mHSPC on ADT ± chemotherapy ± ARSI for the prevention of risk of fracture, denosumab 60 mg every 6 months is advisable. In case of prescriptive ineligibility to therapy with denosumab and lack of reimbursement, the use of another BTA (alendronate 70 mg weekly, risedronate 35 mg weekly or clodronic acid weekly or zoledronic acid 4 mg every 6 months) might be a choice.	93.6	3.2	3.2
	4.3 Before starting and during any hormonal therapy, the levels of vitamin D (≥30 ng/ml) should be evaluated and normalized, regardless of the bone-modifying agent. A calcium intake of about 1000 mg/day or administration of calcium element at the equivalent dose and a daily dose of vitamin D 1500-2000 IU during antiresorptive therapy is mandatory.	90.2	3.3	6.5
5. Patients with mHSPC on ADT+ docetaxel and/or NHT: how long should they be treated with antiresorptive drugs for the prevention of the risk of fractures?	5.1 If no adverse events, antifracture treatment with BTAs should be continued until the diagnosis of castration resistance. After the diagnosis of castration resistance, BTAs should be administered at the same doses and schedule of mCRPC with bone metastases. If no bone metastases occur in mCRPC, the doses and schedule are the same for CTIBL prevention.	93.6	1.6	4.8
6. How to diagnose and monitor the bone health in mHSPC during ADT and docetaxel and/or NHT?	6.1 mHSPC patients should be monitored for metastatic disease by scintigraphy, CT scan or any other evaluation at physician's choice. Moreover, bone health monitoring should be carried out in the same way as nmHSPC (monitor the following: vitamin D; serum calcium and PTH; DEXA scan with trabecular bone score, if available; if possible: bone turnover markers; height, weight and BMI and body composition. In case of back pain or height loss, carry out a spine radiography).	83.6	3.3	13.1
7. For patients who are already being treated for previous osteoporosis and who are candidates for ADT and docetaxel and/or NTH for mHSPC, which treatment is recommended?	7.1 Patients should continue the same treatment for previous osteoporosis, as long as it involves calcium and vitamin D supplementation and BPs (alendronate 70 mg weekly or clodronic acid weekly or zoledronic acid every 6 months) or denosumab 60 mg every 6 months.	88.5	3.3	8.2
	7.2 Patients mHSPC in treatment with BPs for previous osteoporosis should be switched to denosumab 60 mg every 6 months for prevention of fragility fractures.	59	18	23

ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; BMD, bone mineral density; BMI, body mass index; BPs, bisphosphonates; BTAs, bone-targeting agents; CT, computed tomography; CTIBL, cancer treatment-induced bone loss; DEXA, dual-energy X-ray absorptiometry; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NHT, new hormone therapies; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PTH, parathyroid hormone; SREs, skeletal-related events.

Table 3. Non-metastatic castration-resistant prostate cancer

Question	Statement	Level of consensus		
		Agree (%)	Disagree (%)	Uncertain (%)
1. Among patients with nmCRPC receiving ADT ± ARSI, which are those at risk of fracture?	1.1 All patients receiving ADT ± ARSI should be treated with drugs with evidence of anti-fracture efficacy.	88.9	1.6	9.5
2. In males affected by nmCRPC on ADT ± ARSI, which are the drugs to be used for the reduction of the risk of fracture?	2.1 Patients with nmHSPC treated for bone health and become nmCRPC should continue treatment for bone health.	90.2	3.3	6.5
	2.2 In patients with nmCRPC on ADT ± ARSI, for the prevention of risk of fracture, denosumab 60 mg every 6 months is advisable. In case of prescriptive ineligibility to therapy with denosumab and/or lack of reimbursement, the choice of another BTA (alendronate 70 mg weekly, risedronate 35 mg weekly or ZA 4 mg every 6 months) might be a choice.	87.4	6.3	6.3
	2.3 Before starting and during any hormonal therapy, the levels of vitamin D (≥30 ng/ml) should be evaluated and normalized, regardless of the bone-modifying agent.	88.6	1.6	9.8
	2.4 The administration of calcium and daily dose of vitamin D 1500-2000 IU, to reach and maintain the value between 30 ng/ml and 50 ng/ml (75 nmol/l), during antiresorptive therapy is mandatory.	90.2	0	9.8
	2.5 The modalities for diagnosis and monitoring of bone health are the same for nmHSPC and nmCRPC disease.	93.4	0	6.6
	2.6 Patients who have suboptimal response to BPs with incident fracture, declining BMD or persistently low BMD could be switched to denosumab 60 mg every 6 months.	75.4	1.6	23
3. Is it necessary to intensify treatment for bone health in high-risk nmCRPC patients receiving ADT and ARSI compared to low-risk nmCRPC patients receiving ADT alone?[27]	3.1 No different treatment for bone health is advisable in high-risk and low-risk nmCRPC.	84.1	1.6	14.3
4. In high-risk nmCRPC, can the choice of the type of ARSI be influenced by factors related to bone health?	4.1 In high-risk nmCRPC patients considered at high risk of fracture due to obesity, age, sarcopenia or previous osteoporotic fractures and low bone mass, treatment with darolutamide should be preferred to enzalutamide or apalutamide based on the results of the registration trials.	54.1	11.5	34.4
5. In high-risk nmCRPC patients, can the choice of ARSI type influence bone health treatment?	5.1 Patients receiving ARSI in combination with ADT for high-risk nmCRPC should receive bone health treatment regardless of the type of ARSI used, to reduce the incidence of non-pathological fractures.	83.6	8.2	8.2
6. In high-risk nmCRPC, can it be appropriate to carry out a fall risk assessment before deciding on the choice of the type of ARSI to be used?	6.1 Physicians should incorporate fall risk model and body composition by DEXA (for sarcopenia diagnosis) in clinical practice, especially in patients taking high-risk medications or patients with preexisting conditions who have a high risk of fall.	82	1.6	16.4
7. For how long should patients in ADT ± ARSI for nmCRPC be treated with denosumab or BTAs for the prevention of the risk of fractures?	7.1 Treatment with BPs or denosumab should be carried out until the development of mCRPC, and then shifted to the doses and schedules of bone mCRPC.	78.7	1.6	19.7
8. Are there any safety concerns for long-term denosumab and BPs?[28]	8.1 BTAs maintain a favorable efficacy and bone safety profile during long-term treatment with a low absolute risk for serious complications.	78.7	6.6	14.7

ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; BMD, bone mineral density; BPs, bisphosphonates; BTAs, bone-targeting agents; DEXA, dual-energy X-ray absorptiometry; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; nmHSPC, non-metastatic hormone-sensitive prostate cancer; ZA, zoledronic acid.

Table 4. Metastatic castration-resistant prostate cancer

Question	Statement	Level of consensus		
		Agree (%)	Disagree (%)	Uncertain (%)
1. Among patients on treatment for mCRPC, who are those at risk of pathological and fragility fracture?[28]	1.1 All patients with mCRPC and bone metastases should be treated with bone-protecting agents with the aim of SRE reduction as well as to prevent CTIBL and, consequently, the risk of fragility fractures.	93.6	1.6	4.8
	1.2 All patients affected by mCRPC without bone metastases should be treated with bone-protecting agents with the aim to reduce CITBL and, consequently, the risk of fragility fractures.	83.9	6.4	9.7
	1.3 In patients with mCRPC without bone metastases, bone health should be treated, assessed and monitored as in nmCRPC patients.	92	0	8
2. In males affected by mCRPC, which drugs should be used for the reduction of the risk of SREs and for the prevention of CTIBL fragility fracture?[29]	2.1 Denosumab (120 mg every 4 weeks) should be used in patients with mCRPC as it may delay the onset of SREs.	92	3.2	4.8
	2.2 ZA is considered the BP of choice in patients with mCRPC as it may delay the onset of SREs. ZA at a dosage of 4 mg every 4 weeks is considered the standard, while higher doses are not recommended.	91.9	3.2	4.8
	2.3 Vitamin D and calcium supplementation is mandatory during treatment with BTAs. The administration of calcium and daily dose of vitamin D 1500-2000 IU after a load dose (5000 UI/day for 30 days), to reach and maintain the value between 30 ng and 50 ng/ml (75 nmol/l), during antiresorptive therapy is mandatory.	95.2	1.6	3.2
3. Who should be treated with denosumab and who should be treated with ZA?[30]	3.1 The physician's choice between ZA and denosumab should consider comorbidities (i.e. renal impairment) and patient characteristics (i.e. easy vascular access, home therapy).	100	0	0
	3.2 Denosumab might be considered the preferred option in mCRPC patients with bone metastases according to the demonstration of reduction in SREs. However, the choice between denosumab and ZA could be based on many factors: direct costs (drug price for the health care system), indirect costs (commitment of health care structures), individual risk of side-effects (renal toxicity, ONJ, hypocalcemia) and preferences of the patient.	84.1	6.4	9.5
4. When should BTAs be started in patients with mCRPC?[31]	4.1 In mCRPC patients, bone-protecting agents should be started at the dose and schedule for SREs prevention at the time of the first metastasis diagnosis, even if already used to prevent CTIBL, in order to reduce incidence of SREs.	88.7	4.8	6.4
	4.2 Greater awareness of physicians about the importance of BTAs is needed to improve their use in patients with mCRPC and bone metastases.	98.4	0	1.6
5. How long should patients be treated with BTAs?[32]	5.1 In mCRPC after 12-15 months of treatment with ZA every 4 weeks, the shift to a 12-week schedule of ZA could be considered, after assessment of the risk-benefit ratio for the individual patient (e.g., burden of bone metastases, systemic disease control).	80.6	0	19.4
	5.2 Treatment with denosumab should be continued throughout the course of the disease because stopping it may expose to pathological and fragility fracture risk. After denosumab discontinuation, shift to ZA every 4 or every 12 weeks can be considered.	77.8	9.5	12.7
6. The switch from ZA to denosumab: when and how to do it?[33]	6.1 Switch from ZA to denosumab should be considered in patients who develop renal failure during ZA treatment or in patients who experience a new SRE during ZA.	82.3	1.6	16.1
	6.2 Switch from ZA to denosumab can be carried out after 4 weeks from the last ZA administration without adding adverse events, except for ONJ risk due to prolonged BTA exposure. For this reason, a	92	3.2	4.8

Continued

Table 4. Continued

Question	Statement	Level of consensus		
		Agree (%)	Disagree (%)	Uncertain (%)
	close attention to oral cavity monitoring should be taken.			
7. Should ZA or denosumab therapy be used to reduce bone pain?[34]	7.1 BPs and denosumab should be prescribed for the prevention of SREs, but an adequate treatment for pain should be added because the administration of BTAs did not demonstrate an analgesic effect compared to placebo.	87.1	4.8	8.1
8. Radiometabolic therapies in mCRPC patients: why and how to pay attention to bone health?[35,36]	8.1 Before, during and after treatment with radium-223, bone health should be monitored. Radium-223 may be interrupted or stopped if fragility fractures occur.	82.3	3.2	14.5
	8.2 Before starting and during treatment with radium-223, BTAs (denosumab 120 mg or ZA every 14 weeks) should be administered to protect bone from pathological and fragility fractures.	87.1	0	12.9
9. How to diagnose and monitor the bone health in mCRPC?	9.1 Monitor metastases by scintigraphy, NMR or any other evaluation at physician's discretion and monitor bone health by assessing the fracture risk as in non-metastatic disease (monitor: vitamin D; serum calcium and PTH; DEXA scan with trabecular bone score, if available; if possible: bone turnover markers; height, weight, BMI and body composition. In case of back pain or height loss, carry out a spine radiography). Closer attention should be paid to vitamin D, serum calcium and PTH serum levels because of the higher risk of hypocalcemia during administration of ZA or denosumab at the dose for SRE prevention.	96.8	1.6	1.6
10. In mCRPC patients treated with antiresorptive drugs (BPs, denosumab) for SRE prevention, is an oral cavity assessment recommended before starting therapy, in order to reduce the risk of subsequent MRONJ?	10.1 Before starting treatment with BPs or denosumab with schedule for SRE prevention, adequately informed patients have to carry out a dental visit to evaluate their oral health, to set up an adequate prevention program and possibly treat local pathologies before starting BTA therapy.	100	0	0
11. How to manage any dental procedures that may be necessary during antiresorptive treatments for bone metastases in mCRPC?[37]	11.1 Plan an assessment by the prescriber (high risk versus low risk of SREs) and by the dentist (high risk versus low risk of post-extraction complications) to determine the need for a precautionary suspension of ZA or denosumab before and after the dental procedure.	93.5	0	6.5
	11.2 No definitive data have been published and, especially with ZA, there is no safe timing for invasive oral/dental procedures due to its mechanism of action. If procedure is urgent, a suspension frequently applied of ZA or denosumab consists of a period of 4 weeks, at least, from the last assumption before any elective invasive oral or dental procedures. BTA re-assumption should occur not before 6 weeks and only after a complete healing assessed by the dentist.	87.3	3.2	9.5

BMI, body mass index; BPs, bisphosphonates; BTAs, bone-targeting agents; CTIBL, cancer treatment-induced bone loss; DEXA, dual-energy X-ray absorptiometry; mCRPC, metastatic castration-resistant prostate cancer; MRONJ, medication-related osteonecrosis of the jaw; NMR, nuclear magnetic resonance; ONJ, osteonecrosis of the jaw; PTH, parathyroid hormone; SREs, skeletal-related events; ZA, zoledronic acid.

mass of 16% and a reduction in lean body mass (LBM) of 6%. Similarly, recent data from the BONENZA study show that after 18 months of enzalutamide, fat body mass increases by 22% and LBM decreases by 6%.[42]

Androgens regulate bone remodeling units by playing a role in the achievement of peak bone mass and the maintenance of bone integrity. BMD loss occurs during the first years of ADT as a consequence of the rapid decrease in androgens and estradiol[43] and is associated with an increase in bone turnover markers, within 3-6 weeks.[44]

An exploratory substudy of a phase II randomized study with ADT with or without apalutamide suggests that 3 months of ADT in non-metastatic PCa patients results in early bone loss.[45] The addition of apalutamide does not seem to further influence bone loss at 3 months, even if an impact with longer follow-up cannot be excluded. The use of antagonists of luteinizing hormone-releasing hormone (LHRH) leads to a deeper and sustained suppression of testosterone levels than agonists of LHRH, whose consequences on bone loss and body composition are poorly understood.[46]

The distal radius is the strongest predictor of fracture risk in the male population because it is the site of the greatest decline in bone microarchitecture during long-term ADT.[43,47,48]

Microarchitectural changes and BMD measured by dual-energy X-ray absorptiometry (DEXA) are the structural basis of bone fragility fractures in men undergoing ADT. Given these observations, PCa treatment has undergone significant changes in clinical practice, leading to the need for consensus and detailed recommendations to optimize BH in patients with PCa.

The major uncertainties/controversies in bone preventing therapy in patients with PCa have been identified and prioritized, facilitating our focus on both unmet clinical issues with insufficient evidence as well as controversial clinical issues with sufficient evidence for clinical guideline development for the management of these patients.

The panelists agreed that in men with nmHSPC and nmCRPC, even hormone therapy alone constitutes a sufficient fracture risk and bone-targeting agents (BTA) treatment should be initiated *ab initio* in primary prevention.

All mHSPC (with or without bone metastases) and mCRPC (without bone metastases) patients receiving ADT ± chemotherapy ± NHT should be treated with BTA, regardless of individual fracture risk. BTA should be administered at the beginning of ADT, according to the schedule and dosage for the prevention of cancer treatment-induced bone loss (CTIBL), and in principle, not with the same dosage used for the prevention of metastatic bone skeletal-related events (SREs), although each case should be evaluated.

In this setting, in fact, no study demonstrates the efficacy of denosumab or other BTAs in pathological SRE reduction. Early treatment with zoledronic acid (ZA) yielded no benefit in terms of time to first SREs and overall survival in the STAMPEDE and in the ZAPCA trials.[49,50] Recently, an analysis of routinely collected health care data from the STAMPEDE docetaxel and ZA comparisons have been presented with the aim to quantify fracture incidence in men with HSPC recruited to STAMPEDE and to evaluate the impact of adding ZA or docetaxel on fracture risk. In these analyses for the first time, ZA significantly reduced the risk of fracture-related hospitalizations in mHSPC patients. Although this analysis supports the use of high doses of ZA for the reduction of fracture risk, it would be not sufficient to formalize a clinical recommendation. Long-term effects on BH and fracture risk were not formally collected within the STAMPEDE trial; consequently, the retrospective and lack of pre-planning of these results do not allow to provide an unequivocal and definitive opinion on the use of high doses of ZA in mHSPC patients to date.[51]

The panelists agreed to use denosumab 60 mg/6 months, or bisphosphonates (alendronate, risedronate, ZA), with vitamin D and calcium supplementation, normalizing pre-treatment vitamin D levels (calcium and vitamin D supplementation alone are not sufficient). Antiresorptive therapy should be continued throughout the period of continuation of ADT ± NHT. In patients with nmHSPC during adjuvant treatment with ADT, possible continuation of BTA at the end of ADT should be evaluated based on individual fracture risk: if the patient has not developed fragility fractures during ADT and has no additional risk factors, antiresorptive treatment could be discontinued, continuing with BH monitoring. Otherwise, i.e. in high-risk patients, bisphosphonate or denosumab therapy as well as BH monitoring should be continued, especially if treated with denosumab, to avoid rebound risk. In addition, the shift from bisphosphonates to denosumab should be considered in case of suboptimal response (fragility fractures or decline in BMD) when monitoring BH. Similarly, patients who discontinue denosumab and develop bone loss or fragility fractures despite bisphosphonates may be retreated with denosumab. In patients with mHSPC, treatment with BTA should be continued until mCRPC is diagnosed, then continued according to the indications for the mCRPC setting. All mCRPC patients with bone metastases should be treated with BTA from diagnosis in order to both reduce SREs and prevent CTIBL, without analgesic purpose. The drugs to be used are denosumab 120 mg every 28 days, or ZA 4 mg every 28 days with vitamin D and calcium supplementation. The choice must consider comorbidities and individual characteristics of the patient. After 12/18 months of ZA, it is possible to consider a 3-month schedule. For patients who develop renal insufficiency or ongoing SRE on ZA, consider shift to denosumab, to be started 4 weeks after the last ZA administration. The panelists agreed that all patients receiving radium-223 should be treated with BTA. In case of fragility fractures, it is mandatory to discontinue radium-223.

Androgen deprivation may have implications in terms of sarcopenia and frailty in general. Androgen deprivation leads to skeletal muscle impairment as a result of an imbalance between muscle atrophy activation (which is regulated largely by the ubiquitin—proteasomes stem and the autophagy/lysosomal pathways) and muscle growth (which is regulated by androgen receptor/β-catenin as well as transforming growth factor-β/SMAD, and insulin-like growth factor 1/Akt/mammalian target of rapamycin signaling).[52,53]

ADT leads to profound hypogonadism as well as observed with aging and frailty, which is accelerated by the accumulation of age-related medical comorbidities and obesity. Literature data demonstrate that men on ADT reported an increase in fatigue, decline in the QoL and decline in physical activity and physical function compared with control groups.[54-57] However, it is still unclear whether ADT-related muscle mass loss affects an individual's physical functioning in terms of independence and risk of falls. In men on ADT, lower LBM is associated with greater fat mass, leading to 'sarcopenic obesity'. These body composition changes related to ADT occur maximally over the first 6 months with little change observed thereafter[58,59] and the estimated value is of around 9.5% and 2% in increase in fat mass and in decrease in LBM, respectively. It is noteworthy that simple ADT is no longer the standard of treatment for patients with mHSPC. Using modern NHT, body composition

changes become more important. NHT-treated patients are more prone to sarcopenic obesity because their fat body mass is expected to increase by up to 22% while their LBM is expected to decrease by 6%.[42] Given these observations, supplementing treatment with assisted physical activity programs and periodic nutritional assessments is of paramount importance to reduce the risk of sarcopenia and improve overall BH. Individually supervised physical exercise may be guided by the heterogeneous variation of body composition, assessed by DEXA scan, in relation to different body districts in patients treated with ADT, as evidenced recently.[60]

The main strengths of this consensus embrace the inclusion of the MEET-URO group, the major Italian oncourologic cooperative group, in collaboration with the major Italian endocrinologist experts on BH. This allowed a more targeted, standardized and systematic approach of including controversies that have been identified and evaluated by the panelists. However, some recommendations are not fully evidence-based ones. In these cases, experts considered the available literature data to achieve a unique statement, recognizing a lack of literature data concerning the impact on BH of several therapeutic innovations available to date in PCa. The Bone Health and Body Composition Consensus in PCa gathered expert opinions on these topics focusing on that lacking sufficient literature data or for which there is conflicting interpretation of the data to guide treatment decisions.

Although the Delphi method offers several advantages, it also has its limitations. A first limitation concerns the number of panelists involved: the selection of the limited number of experts included in the present panel may have provided a partial rather than an overall picture of the national scenario. However, the sample of panelists was carefully selected to be as representative as possible of the experts on this topic in Italy. Another limitation would be the possibility of groupthink, as the experts might tend to agree with the prevailing opinion within the group: to avoid this, the panelists voted simultaneously, and remotely via a web link. In this way, the answers were given in complete autonomy. A third limitation could be the definition of consensus. To ensure maximum replicability, the statement was accepted if the agreement was ≥75%. In addition, the 5-point Likert scale was chosen over the 9-point scale in order to minimize the spread of votes cast by the members of the expert panel.

In areas lacking major consensus including patients with nmHSPC treated with short- or long-term ADT, the evaluation of these topics in prospective clinical trials is especially urgent. If pharmaceutical companies are not interested in exploring these high-priority topics, then academic clinical researchers need to step in and urgently seek funding for clinically relevant trials such as studies on bone health management in nmHSPC patients treated with short-term ADT.

Future studies are warranted to address if early biomarkers of bone loss are able to predict fracture risk and can be implemented in clinical practice for follow-up of BH in PCa patients treated with hormonal therapies.

Finally, the Bone Health and Body Composition Consensus in PCa did not address all patient-related factors, such as comorbidities, compliance and drug—drug interaction in men with polipharmacotherapy, preferences that may contribute to the treatment approach. Over time, PCa has become an intricate disease that mandates a comprehensive understanding and a multidisciplinary approach. Consequently, several recommendations are limited not only by the clinical scenario but also could require discussion in multidisciplinary team meetings.

DISCLOSURE

DS reports fee from advisory boards by AstraZeneca, Lilly, Daiiki-Sanchio, Astellas, Janssenn, Recordati, Gilead, Pfizer, MSD, Novartis, BMS, Roche, EISAI and Ipsen. MDM reports honoraria from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, GlaxoSmithKline, Amgen, Merck, Takeda for consultancy or participation to advisory boards; direct research funding from Tesaro/GlaxoSmithKline; institutional funding for work in clinical trials/contracted research from Beigene, Exelixis, MSD, Pfizer and Roche. UDG: consulting or advisory role for Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, DompéFarmaceutici, Eisai, Ipsen, Janssen, Merck KgaA, MSD, Novartis and Pfizer; research funding (institution) from AstraZeneca, Roche and Sanofi; and travel accommodations from AstraZeneca, Ipsen and Pfizer. All other authors have declared no conflicts of interest.

REFERENCES

1. I Numeri del Cancro in Italia, 2021. Available at https://www.aiom.it/wp-content/uploads/2021/10/2021_NumeriCancro_web.pdf. Accessed September 23, 2023.
2. Rhee H, Gunter JH, Heathcote P, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int*. 2015;115(suppl 5):3-13.
3. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol*. 2015;5:825-836.
4. Wang A, Obertová Z, Brown C, et al. Risk of fracture in men with prostate cancer on androgen deprivation therapy: a population-based cohort study in New Zealand. *BMC Cancer*. 2015;15:837.
5. Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. *Cancer*. 2009;115(11):2388-2399.
6. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol*. 2000;5:578-583.
7. Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26:v69-v77.
8. Santini D, Berruti A, Di Maio M, et al. Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion. *ESMO Open*. 2020;5(2):e000652.

9. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol*. 2002;167:2361-2367; discussion 2367.

10. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology*. 2004;4:742-745.

11. Strong AL, Burow ME, Gimble JM, Bunnell BA. Concise review: the obesity cancer paradigm: exploration of the interactions and crosstalk with adipose stem cells. *Stem Cells*. 2015;33(2):318-326.

12. Trevellin E, Scarpa M, Carraro A, et al. Esophageal adenocarcinoma and obesity: peritumoral adipose tissue plays a role in lymph node invasion. *Oncotarget*. 2015;6(13):11203-11215.

13. Colleluori G, Perugini J, Barbatelli G, Cinti S. Mammary gland adipocytes in lactation cycle, obesity and breast cancer. *Rev Endocr Metab Disord*. 2021;22(2):241-255.

14. Carraro A, Trevellin E, Fassan M, et al. Esophageal adenocarcinoma microenvironment: peritumoral adipose tissue effects associated with chemoresistance. *Cancer Sci*. 2017;108(12):2393-2404.

15. Dalla Volta A, Caramella I, Di Mauro P, et al. Role of body composition in the prediction of skeletal fragility induced by hormone deprivation therapies in cancer patients. *Curr Oncol Rep*. 2023;25(10):1141-1152.

16. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005;2:154-164.

17. Greenspan SL, Nelson JB, Trump DL, et al. Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. *J Clin Oncol*. 2008;26(27):4426-4434.

18. Poon Y, Pechlivanoglou P, Alibhai SMH, et al. Systematic review and network meta-analysis on the relative efficacy of osteoporotic medications: men with prostate cancer on continuous androgen-deprivation therapy to reduce risk of fragility fractures. *BJU Int*. 2018;121(1):17-28.

19. Alibhai SMH, Zukotynski K, Walker-Dilks C. Bone health and bone-targeted therapies for nonmetastatic prostate cancer. *Ann Intern Med*. 2018;6:459-460.

20. Bertoldo F, Cianferotti L, Di Monaco M, et al. Definition, assessment, and management of vitamin D inadequacy: suggestions, recommendations, and warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). *Nutrients*. 2022;14(19):4148.

21. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*. 2013;368(14):1314-1325.

22. Briot K, Paccou J, Beuzeboc P, et al. French recommendations for osteoporosis prevention and treatment in patients with prostate cancer treated by androgen deprivation. *Joint Bone Spine*. 2019;1:21-28.

23. Campisi G, Mauceri R, Bertoldo F, et al. Medication-Related Osteonecrosis of Jaws (MRONJ) prevention and diagnosis: Italian consensus update 2020. *Int J Environ Res Public Health*. 2020;17(16):5998.

24. Zheng R, Byberg L, Larsson SC, Höijer J, Baron JA, Michaëlsson K. Prior loss of body mass index, low body mass index, and central obesity independently contribute to higher rates of fractures in elderly women and men. *J Bone Miner Res*. 2021;36(7):1288-1299.

25. Ohtaka A, Aoki H, Nagata M, et al. Sarcopenia is a poor prognostic factor of castration-resistant prostate cancer treated with docetaxel therapy. *Prostate Int*. 2019;7(1):9-14.

26. Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol*. 2014;32(11):1143-1150.

27. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379(9810):39-46.

28. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;7:513-523.

29. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813-822.

30. Jiang L, Cui X, Ma H, Tang X. Comparison of denosumab and zoledronic acid for the treatment of solid tumors and multiple myeloma with bone metastasis: a systematic review and meta-analysis based on randomized controlled trials. *J Orthop Surg Res*. 2021;16(1):400.

31. Body JJ, von Moos R, Rider A, et al. A real-world study assessing the use of bone-targeted agents and their impact on bone metastases in patients with prostate cancer treated in clinical practice in Europe. *J Bone Oncol*. 2019;14:100212.

32. Clemons M, Liu M, Stober C, et al. Two-year results of a randomised trial comparing 4- versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. *J Bone Oncol*. 2021;30:100388.

33. Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol*. 2009;10:1564-1571.

34. Meulenbeld HJ, van Werkhoven ED, Coenen JL, et al. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). *Eur J Cancer*. 2012;16:2993-3000.

35. EORTC. Preliminary results confirm that the addition of bone-protecting agents to radium-233 (Ra-233) treatment can limit fractures in metastatic castration resistant prostate cancer patients. Available at https://www.eortc.org/blog/2019/05/31/preliminary-results-confirm-that-the-addition-of-bone-protecting-agents-to-radium-233-ra-233-treatment-can-limit-fractures-in-metastatic-castration-resistant-prostate-cancer-patients-2/. Accessed July 14, 2023.

36. Fizazi K, Herrmann K, Krause BJ, et al. Health-related quality of life and pain outcomes with [(177)Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2023;6:597-610.

37. Heggendorn FL, Leite TC, Cunha KS, et al. Bisphosphonate-related osteonecrosis of the jaws: report of a case using conservative protocol. *Spec Care Dentist*. 2016;36(1):43-47.

38. Cannata DH, Kirschenbaum A, Levine AC. Androgen deprivation therapy as primary treatment for prostate cancer. *J Clin Endocrinol Metab*. 2012;2:360-365.

39. Pezaro C, Mukherji D, Tunariu N, et al. Sarcopenia and change in body composition following maximal androgen suppression with abiraterone in men with castration-resistant prostate cancer. *Br J Cancer*. 2013;109(2):325-331.

40. Grossmann M, Hamilton EJ, Gilfillan C, Bolton D, Joon DL, Zajac JD. Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. *Med J Aust*. 2011;6:301-306.

41. Grossmann M, Cheung AS, Zajac JD. Androgens and prostate cancer; pathogenesis and deprivation therapy. *Best Pract Res Clin Endocrinol Metab*. 2013;4:603-616.

42. Tombal B, Borre M, Rathenborg P, et al. Long-term antitumor activity and safety of enzalutamide monotherapy in hormone naïve prostate cancer: 3-year open label followup results. *J Urol*. 2018;2:459-464.

43. Hamilton EJ, Ghasem-Zadeh A, Gianatti E, et al. Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. *J Clin Endocrinol Metab*. 2010;12:E456-E463.

44. Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest*. 2000;106(12):1553-1560.

45. David K, Devos G, Narinx N, et al. Changes in bone and mineral homeostasis after short-term androgen deprivation therapy with or without androgen receptor signalling inhibitor - substudy of a single-centre, double blind, randomised, placebo-controlled phase 2 trial. *EBioMedicine*. 2023;97:104817.

46. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187-2196.

47. Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. Bone density and fracture risk in men. *J Bone Miner Res*. 1998;13(12):1915-1923.

48. Preston DM, Torréns JI, Harding P, Howard RS, Duncan WE, McLeod DG. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis*. 2002;4:304-310.

49. Kamba T, Kamoto T, Maruo S, et al. A phase III multicenter, randomized, controlled study of combined androgen blockade with versus without zoledronic acid in prostate cancer patients with metastatic bone disease: results of the ZAPCA trial. *Int J Clin Oncol*. 2017;1:166-173.

50. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-1177.

51. Jones C, Dutey-Magni P, Murphy LR, et al. 1768MO Incidence of fracture related hospitalisations in men with de novo high risk localised and metastatic hormone sensitive prostate cancer: analysis of routinely collected healthcare data from the STAMPEDE docetaxel and zoledronic acid comparisons. *Ann Oncol*. 2023;34:S956-S957.

52. Bhasin S, Jasuja R, Tu P, Storer TW, Guo W. Novel strategies for improving physical function. *Horm Res Paediatr*. 2011;76(suppl 1):17-23.

53. Serra C, Sandor NL, Jang H, et al. The effects of testosterone deprivation and supplementation on proteasomal and autophagy activity in the skeletal muscle of the male mouse: differential effects on high-androgen responder and ow-androgen responder muscle groups. *Endocrinology*. 2013;154(12):4594-4606.

54. Bylow K, Dale W, Mustian K, et al. Falls and physical performance deficits in older patients with prostate cancer undergoing androgen deprivation therapy. *Urology*. 2008;72(2):422-427.

55. Soyupek F, Soyupek S, Perk H, Ozorak A. Androgen deprivation therapy for prostate cancer: effects on hand function. *Urol Oncol*. 2008;2:141-146.

56. Clay CA, Perera S, Wagner JM, Miller ME, Nelson JB, Greenspan SL. Physical function in men with prostate cancer on androgen deprivation therapy. *Phys Ther*. 2007;10:1325-1333.

57. Bylow K, Hemmerich J, Mohile SG, Stadler WM, Sajid S, Dale W. Obese frailty, physical performance deficits, and falls in older men with biochemical recurrence of prostate cancer on androgen deprivation therapy: a case-control study. *Urology*. 2011;77(4):934-940.

58. Levy ME, Perera S, van Londen GJ, Nelson JB, Clay CA, Greenspan SL. Physical function changes in prostate cancer patients on androgen deprivation therapy: a 2-year prospective study. *Urology*. 2008;4:735-739.

59. Boxer RS, Kenny AM, Dowsett R, Taxel P. The effect of 6 months of androgen deprivation therapy on muscle and fat mass in older men with localized prostate cancer. *Aging Male*. 2005;8:207-212.

60. Dalla Volta A, Palumbo C, Zamboni S, et al. Heterogeneity in regional changes in body composition induced by androgen deprivation therapy in prostate cancer patients: potential impact on bone health-the BLADE study. *J Endocrinol Invest*. 2024;47:335-343.

APPENDIX A

List of Meet-Uro and AIOM experts who have contributed to the consensus. We thank all of them.

Name and surname	Affiliation (country)	Speciality	Degree
Amelia Altavilla	Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy	Oncology	MD, Oncologist
Francesco Atzori	Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy	Oncology	MD, Oncologist
Giuseppe Luigi Banna	Faculty of Science and Health, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK	Oncology	MD, Oncologist, Honorary Associate Professor
Sandro Barni	Oncology Unit, ASST Bergamo ovest, Treviglio, Italy	Oncology	MD, Oncologist (Retired)
Umberto Basso	Istituto Oncologico Veneto IOV IRCCS, Padova, Italy, Italy	Oncology	MD, Oncologist
Matteo Bauckneht	IRCCS Ospedale Policlinico San Martino, 16132 Genova, Italy	Nuclear Medicine	MD, Specialist in Nuclear Medicine
Rossana Berardi	Clinical Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy	Oncology	MD, Oncologist, Professor
Alfredo Berruti	Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy	Oncology	MD, Oncologist, Professor
Francesco Bertoldo	Emergency Medicine, Department of Medicine, University of Verona, Verona, Italy	Endocrinology	MD, Endocrinologist, Professor
Davide Bimbatti	Department of Medical Oncology, Istituto Oncologico Veneto IOV, IRCCS, Padova, Italy	Oncology	MD, Oncologist
Francesco Boccardo	Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genoa, 16132, Genoa, Italy	Oncology	MD, Oncologist (Retired)
Sebastiano Buti	Medical Oncology Unit, University Hospital of Parma, Parma, Italy	Oncology	MD, Oncologist, Professor
Consuelo Buttigliero	Azienda Ospedaliera Citta' della Salute e della Scienza di Torino, Torino, Italy	Oncology	MD, Oncologist, Professor
Orazio Caffo	Department of Medical Oncology, Santa Chiara Hospital, Trento, Italy	Oncology	MD, Oncologist

Continued

Continued			
Name and surname	**Affiliation (country)**	**Speciality**	**Degree**
Fabio Calabrò	Department of Oncology, San Camillo Forlanini Hospital, Rome, Italy	Oncology	MD, Oncologist
Carlo Cattrini	Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genoa, 16132, Genoa, Italy	Oncology	MD, Oncologist
Francesco Cellini	Dipartimento Universitario Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia Università Cattolica del Sacro Cuore, Roma, Italy	Radiotherapy	MD, Radiation oncologist
Vincenza Conteduca	Department of Medical and Surgical Sciences, Unit of Medical Oncology and Biomolecular Therapy, University of Foggia, Policlinico Riuniti, Foggia, Italy	Oncology	MD, Oncologist
Maria Concetta Cursano	Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy	Oncology	MD, Oncologist
Giulia De Feo	Medical Oncology 4: SSD Internistic & Geriatric Supportive Care, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy	Oncology	MD, Oncologist
Ugo De Giorgi	Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy	Oncology	MD, Oncologist
Giuseppe Di Lorenzo	Oncology Unit, Andrea Tortora Hospital, ASL Salerno, Pagani, Italy	Oncology	MD, Oncologist
Massimo Di Maio	Department of Oncology, University of Turin, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Molinette, Turin, Italy	Oncology	MD, Oncologist, Professor
Marilena Di Napoli	Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy	Oncology	MD, Oncologist
Paola Ermacora	Department of Oncology, Presidio Ospedaliero Universitario Santa Maria della Misericordia, Azienda Sanitaria Universitaria Integrata Friuli Centrale, Udine, Italy	Oncology	MD, Oncologist

Continued

Continued			
Name and surname	**Affiliation (country)**	**Speciality**	**Degree**
Giuseppe Fornarini	Medical Oncology Unit 1, Istituto di ricovero e cura a carattere scientific (IRCCS) Ospedale Policlinico San Martino, Genoa, Italy	Oncology	MD, Oncologist
Lucia Fratino	Division of Medical Oncology C, Centro di Riferimento Oncologico National Cancer Institute, 33081 Aviano, Italy	Oncology	MD, Oncologist
Vittorio Fusco	Oncology Unit and Hospital Translational Medicine Unit, DAIRI Department of Integration, Research and Innovation, Azienda Ospedaliera-Universitaria "SS Antonio E Biagio e Cesare Arrigo", Alessandria, Italy	Oncology	MD, Oncologist and Radiation Oncologist (Retired)
Angela Gernone	University Department of Medical Oncology, Azienda Ospedaliera Policlinico, Bari, Italy	Oncology	MD, Oncologist
Toni Ibrahim	UOC Oncologia A, Policlinico Umberto 1, La Sapienza Università, Rome, Italy	Oncology	MD, Oncologist
Gaetano Lanzetta	Department of Medical Oncology, IRCCS Istituto Romagnolo Per Lo Studio Dei Tumori (IRST) "Dino Amadori", Meldola, Italy	Oncology	MD, Oncologist
Andrea Malgeri	Department of Medical Oncology, Fondazione Policlinico Campus Bio-Medico, 00128 Roma, Italy	Oncology	MD, Resident
Marco Maruzzo	Oncologia 1, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy	Oncology	MD, Oncologist
Cristina Masini	Medical Oncology, Comprehensive Cancer Centre IRCCS - AUSL Reggio Emilia, Reggio Emilia, Italy	Oncology	MD, Oncologist
Carlo Messina	Oncology Unit, ARNAS Civico Di Cristina Benfratelli Hospital, Palermo, Italy	Oncology	MD, Oncologist
Alessandra Mosca	Oncology, Candiolo Cancer Institute, IRCCS-FPO, 10060, Turin, Italy	Oncology	MD, Oncologist
Emanuele Naglieri	Department of Medical Oncology, IRCCS Istituto Tumori "Giovanni Paolo II", Bari 70124, Italy	Oncology	MD, Oncologist
Franco Nolè	European Institute of Oncology IRCCS, Milan, Italy	Oncology and Endocrinology	MD, Oncologist, Endocrinologist
Cinzia Ortega	Oncology, Asl Cn2, Ospedale Michele e Pietro Ferrero, Verduno, Italy	Oncology	MD, Oncologist
Andrea Palermo	Unit of Metabolic Bone and Thyroid Disorders,	Endocrinology	MD, Endocrinologist

Continued

Continued			
Name and surname	**Affiliation (country)**	**Speciality**	**Degree**
	Fondazione Policlinico Universitario Campus Bio-Medico, 00128 Rome, Italy		
Francesco Pantano	Department of Medical Oncology, Campus Bio-Medico University, Rome, Italy	Oncology	MD, Oncologist, Professor
Veronica Prati	Department of Medical Oncology, Ospedale Michele e Pietro Ferrero, Verduno-Azienda Sanitaria Locale CN2, Alba-Bra, 12060 Cuneo, Italy	Oncology	MD, Oncologist
Giuseppe Procopio	Programma Prostata Fondazione Istituto Nazionale Tumori Milano, Milan, Italy	Oncology	MD, Oncologist
Pasquale Rescigno	Translational and Clinical Research Institute, Centre for Cancer, Newcastle University, Newcastle Upon Tyne, UK	Oncology	MD, Oncologist
Michela Roberto	UOC Oncology A, Department of Radiological, Oncological and Anatomo-Pathological Science, Policlinico Umberto I, "La Sapienza" University of Rome, Rome, Italy	Oncology	MD, Oncologist
Sabrina Rossetti	Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, 80138 Naples, Italy	Oncology	MD, Oncologist
Giandomenico Roviello	Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, 50139, Florence, Italy	Oncology	MD, Oncologist, Professor
Daniele Santini	Oncologia Medica A, Policlinico Umberto 1, La Sapienza Università Di Roma, Rome, Italy	Oncology	MD, Oncologist, Professor
Marco Stellato	Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy	Oncology	MD, Oncologist
Rosa Tambaro	Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, 80138 Naples, Italy	Oncology	MD, Oncologist
Ilaria Toma	Unità Operativa Complessa di Oncologia, Azienda Ospedaliera Cardinale G. Panico, 73039 Tricase, Italy	Oncology	MD, Oncologist
Marcello Tucci	Department of Medical Oncology, Cardinal Massaia Hospital, Asti, Italy	Oncology	MD, Oncologist

Continued

Continued			
Name and surname	Affiliation (country)	Speciality	Degree
Anna Amela Valsecchi	Department of Oncology, University of Turin, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Molinette, Turin, Italy	Oncology	MD, Resident
Elena Verzoni	Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian 1, Milan, Italy	Oncology	MD, Oncologist
Elisa Zanardi	UO Clinica Di Oncologia Medica, IRCCS Ospedale Policlinico S. Martino, 16132, Genova, Italy	Oncology	MD, Oncologist
Paolo Andrea Zucali	Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy; Department of Oncology, IRCCS Humanitas Research Hospital, Milan, Italy	Oncology	MD, Oncologist, Professor

APPENDIX B

Summary of all question and statements of the consensus, and of existing literature in each specific setting.

a) *Non metastatic hormone sensitive prostate cancer*

Depending on the risk factors, patient with prostate cancer (PCa) undergoing or not undergoing to curative intent therapy (prostatectomy, radiotherapy +/- Androgen Deprivation Therapy, ADT) without evidence of distant metastatic disease may be a candidate for ADT with LHHRa or gonadotropin-releasing hormone (GnRH) antagonists in the adjuvant setting or at biochemical relapse.

1. Among patients receiving ADT, which are those at risk of fracture?

ADT induces bone impairment and augments bone fragility, and thus the risk of fracture, through two mechanisms: bone turnover increase, which leads to bone mass loss and to qualitative/microarchitectural alterations, and body mass changes, namely increased fat body mass and decreased lean body mass.[1,2] In men, bone remodeling and microstructure are directly regulated by testosterone levels, whereas the development and maintenance of the skeleton are predominantly regulated by estradiol, acting as the main inhibitor of bone resorption. By reducing serum testosterone levels to a castration range of values and serum estradiol levels, ADT is responsible of a rapid increase of bone turnover that results in bone loss and in qualitative/microarchitectural.[3]

Consequently, the fracturing risk of these patients is imminent.[4] In men with PCa treated with ADT, as well as women with breast cancer treated with aromatase inhibitors (AIs), fractures (especially vertebral) typically occur during the first year of therapy, because of the early and rapid qualitative damage caused by the enhanced bone turnover.[4-8] The rate of bone loss recorded immediately after the start of ADT is 4%—4.6% per year, higher than the normal rate of approximately 0.5%—2% per year.[9,10]

Other risk factors for fractures are older age, prior fragility fracture, preexisting osteoporosis, and the rate of bone loss during treatment.[6] However, fracture risk in men on ADT is not often correlated to bone mineral density (BMD)[3] and Dual Energy X-ray Absorptiometry (DEXA) measurements could underestimate fracture risk of these patients,[2,11] confirming it is prominently dependent on the quality microarchitectural bone damage rather than on the low bone mass. However BMD assessment by DEXA often underestimate the risk of fracture in men on ADT, which suggests that it may be due to microarchitectural quality bone damage instead of low bone mass. Qualitative/Microarchitectural bone damage is early and rapid (peak at 6 months) after start ADT and it is not reversible.[3]

Statement 1.1 Adjuvant hormone therapy alone implies sufficient fracture risk to warrant antifracture therapy as primary or secondary prevention, independently from the presence of other fracture risk factors.

Level of consensus: 79.4% agree; 11.1% disagree; 9.5% uncertain

Statement 1.2 All patients receiving short term ADT (3-6 months) should be treated with antifracture prevention therapy.

Level of consensus: 48% agree; 37% disagree; 15% uncertain

Statement 1.3 All patients receiving long term ADT (> 6 months) should be treated with antifracture prevention therapy.

Level of consensus: 88% agree; 2% disagree; 10% uncertain

2. When should antiresorptive therapy be started in patients with PCa starting hormone therapy?

Treatment for the prevention of Cancer treatment induced bone loss (CTIBL) performed upfront is more effective than started later. Evidence literature data of BMD loss prevention[12] and antifracture efficacy[7] are present in randomised control trials where the therapy was started in upfront (or delayed up to 6 months after the start of adjuvant hormone therapy). Furthermore, as ADT induced bone fragility is mainly due to an alteration of bone quality, early administration of bone resorption inhibitors is needed as the impairment of bone quality is irreversible.

Statement 2.1 Bone-targeting agents (BTAs) should be considered immediately from the start of hormonal therapy itself.

Level of consensus: 80% agree; 8.3% disagree; 11.7% uncertain

3. In males affected by PCa on androgen deprivation therapy, which are the drugs to be used for the reduction of the risk of fracture?

All BTAs at all schedules and doses used were able to prevent bone loss and/or improve BMD compared with

placebo.[7,13-15] However, the only agent that demonstrated effective in reducing the incidence of new vertebral fractures is denosumab.[16]

Statement 3.1 *In patients with PCa on ADT for the prevention of risk of fracture denosumab 60 mg/every 6 months is advisable. In case of prescriptive ineligibility to therapy with denosumab and/or lack of reimbursement, the choice of another BTA (alendronate 70 mg/weekly, risedronate 35 mg/weekly or zoledronate acid 4 mg every 6 months) might be a choice.*

Level of consensus: 93.7% agree; 0% disagree; 6.3% uncertain

4. Are vitamin D and calcium supplementations alone sufficient to maintain bone health or prevent fragility fractures in with PCa starting hormone therapy?

Statement 4.1 *Vitamin D and calcium supplementation alone are not sufficient to maintain bone health and to prevent fragility fractures.*[17]

Level of consensus: 76.7% agree; 5% disagree; 18.3% uncertain

Statement 4.2 *Before starting and during any hormonal therapy, the levels of vitamin D ($\geq$30ng/mL) should be evaluated and normalized, regardless of the bone-modifying agent.*[17]

Level of consensus: 91.7% agree; 1.6% disagree; 6.7% uncertain

Statement 4.3 *The administration of calcium and daily dose of Vitamin D 1500$-$ 2000IU, to reach and maintain the value of 30ng/ mL (75nmol/L), during antiresorptive therapy is mandatory.*[17]

Level of consensus: 93.3% agree; 0% disagree; 6.7% uncertain

5. Is intermittent ADT useful for maintaining bone health?

Statement 5.1 *The use of intermittent ADT does not yield a reduction in bone events (osteoporosis or fracture) and use of BTAs should be considered even in patients receiving intermitted ADT.*[18,19]

Level of consensus: 85.7% agree; 8% disagree; 6.3% uncertain

6. How to diagnose and monitor the bone health in nmHSPC during and after ADT?

Even if the increased risk of fracture is often independent of BMD in patients with PCa on ADT, current guidelines recommend the use of BMD, measured through DEXA scan, as a parameter in the assessment of fracture risk among men on ADT.

FRAX score is used in clinical practice to calculate the 10-year probability of osteoporotic fractures by evaluating the following risk factors, besides BMD: age, sex, weight, height, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis and alcohol ($\geq$3 units/ day).[20-23]

However, it was not specifically designed for men receiving ADT and it does not allow adequate risk stratification of this population.

The ultrasound investigation provides two parameters (velocity and attenuation) which evaluate bone mass and structural integrity, mainly used in two sites the phalanges and the calcaneus. Ultrasound parameters have been shown to predict the risk of osteoporotic fractures (femoral and vertebral) no less than lumbar or femoral DEXA but cannot be used for the diagnosis of osteoporosis. Conventional radiology (radiography, spinal MRI, and spinal CT) allows for its diagnosis and characterization of fragility fractures.[24] Bone turnover markers commonly used as overall indicators of skeletal remodelling are bone isoenzyme alkaline phosphatase (B-ALP) and propeptides of collagen type I (PINP), indicators of new bone formation, while serum levels of terminal telopeptides of collagen type I (CTx), marker of bone resorption.

Significant changes in the markers were found just a few weeks after the start of BTAs and could be proposed as tools to evaluate patient adherence to drug treatment.[24]

According to some epidemiological studies they could be useful for estimating the risk of fracture, however they present a wide analytical and biological variability.[24]

Regarding body composition, the guidelines identify low body mass index as an independent fracture risk factor. A recent Italian retrospective study has instead observed a direct correlation between BMI and risk of vertebral fractures suggesting that in the absence of hormones (androgens and estrogens) the interplay between body composition and bone fragility is different from what occurs in physiological conditions.[25]

A small prospective study, which monitored body composition and turnover markers at baseline and after 12 months of treatment with a luteinising hormone-releasing hormone (LHRH) antagonist (degarelix), demonstrated an inverse correlation between changes in ALMI (Appendicular Lean Mass Index, a measurement of muscle mass of both limbs) and CTX changes before and after degarelix. While a direct correlation has been demonstrated between variations of ALMI and B-ALP, these data suggest that the reduction in lean mass induced by hormonal treatment may favor an uncoupling between osteoclastic and osteoblastic activity, contributing to the alteration of bone quality induced by hormonal therapy.[26]

Statement 6.1 *To monitor bone health during androgen deprivation therapy, the following assessments should be performed at baseline and every 12-18 months thereafter: Vitamin D, serum calcium and parathyroid hormone (PTH).*

Level of consensus: 81.7% agree; 5% disagree; 13.3% uncertain

Statement 6.2 *To monitor bone health during androgen deprivation therapy, the following assessments might be performed, if possible, at baseline and every 18 months*

thereafter: DEXA scan (for BMD) and, if available, vertebral morphometry.

Level of consensus: 95.2% agree; 0% disagree; 4.8% uncertain

Statement 6.3 To monitor bone health during androgen deprivation therapy, the following assessments might be performed, if possible, at baseline and every 18 months thereafter: DEXA scan with trabecular bone score (TBS).

Level of consensus: 92.1% agree; 1.6% disagree; 6.3% uncertain

Statement 6.4: To monitor bone health during androgen deprivation therapy, the following assessments should be performed at baseline and every 12-18 months thereafter: Bone turnover markers, height, weight and Body Mass Index (BMI) and body composition (by DEXA, bioelectrical impedance or plicometry) besides body mass index.

Level of consensus: 76.7% agree; 3.3% disagree; 20% uncertain

Statement 6.5 Given the high prevalence of risk factors for fracture independent of hormone therapy and the high prevalence of vertebral fractures already present at the time of cancer diagnosis, all subjects with PCa should be investigated for the presence of fragility fractures by traditional radiography at baseline.

Level of consensus: 60% agree; 15% disagree; 25% uncertain

Statement 6.6 Patients with nmHSPC receiving ADT may benefit from a supervised physical activity program in terms of bone health regardless of whether they are receiving antiresorptive therapy or not.

Level of consensus: 98.3% agree; 0% disagree; 1.7% uncertain

7. **In nmHSPC patients treated with antiresorptive drugs (bisphosphonates, BPs and denosumab) for bone health, is an oral cavity assessment recommended before starting therapy, to reduce the risk of subsequent medication-related osteonecrosis of the jaw (MRONJ)?**

No MRONJ cases occurred during FREEDOM trial. Only 13 adjudicated cases of MRONJ were observed during the Extension FREEDOM (5.2 per 10,000 subject-years), of which 9 had an inciting event such as tooth extraction or denture involvement. Of the MRONJ lesions, 11/13 were assessed as mild or moderate grade.[27-29]

Statement 7 Before starting treatment with BPs or denosumab, adequately informed patients have to perfom a dental visit to evaluate their oral health, to set up an adequate prevention program and possibly treat local pathologies.

Level of consensus: 85% agree; 8.3% disagree; 6.7% uncertain

8. **How to manage any dental procedures that may be necessary during anti-resorptive treatments for bone health in nmHSPC?**

Statement 8.1 In patients in treatment with BPs, their long half-life leads to an inhibition effect on osteoclastic function of unpredictable duration over time, even after a

single administration. A temporary suspension of BPs (at least 7 days before and at least 6-8 weeks after the surgical procedure) could reduce their anti-angiogenic effect on the soft tissues, in order to therefore favour the vascularization of the healing tissues. The resumption of pharmacological therapy will be possible 6-8 weeks after the dental surgical procedure, once the post-surgical oral site has healed.[30-32]

Level of consensus: 83.3% agree; 5% disagree; 11.7% uncertain

Statement 8.2 In patients in treatment with denosumab, the urgency of the surgical procedure must first be assessed. In the presence of urgent invasive dental procedures that cannot be postponed (for example tooth extraction), it is advisable to perform the dental surgical maneuvers 3 weeks after the last administration of denosumab 60 mg and to apply ad hoc medical-surgical protocol. In the presence of invasive dental procedures that can be postponed (for example tooth extractions, implantology), it is advisable to perform the surgical maneuvers starting from the end of the 5th month after the last administration of denosumab. The resumption of pharmacological therapy will be possible 6-8 weeks after the dental surgical procedure, once the post-surgical oral site has healed.[30-32]

Level of consensus: 91.7% agree; 0% disagree; 8.3% uncertain

9. **Patients on adjuvant ADT: how long should be treated with BTAs for the prevention of the risk of fractures?**

Fracture rates remain high throughout the duration of hormone therapy, and a significant reduction in fracture rates is observed only after discontinuation. However, other individual risk factors (obesity, age, sarcopenia, previous osteoporotic fractures) maintain an elevated risk of fractures even after discontinuation of adjuvant hormone therapy.[33,34]

Statement 9 For patients on adjuvant ADT, therapy with antiresorptive drugs should be continued at least for the entire duration of the adjuvant hormone therapy itself. After the end of adjuvant androgen deprivation therapy, the risk fracture of the patient should be reassessed to evaluate the possible continuation of antiresorptive therapy.

Level of consensus: 93.3% agree; 0% disagree; 6.7% uncertain

10. **How to continue denosumab or BPs beyond the duration of adjuvant ADT? Is there maximum treatment duration and what to do after discontinuation?**

Denosumab discontinuation might be considered in several clinical circumstances: patient remains fracture-free and has achieved low fracture risk; patient has suboptimal response to denosumab with incident fracture, declining BMD, or persistently low BMD; or patient develops hypersensitivity or other adverse effects to denosumab, such as osteonecrosis of the jaw (ONJ). However, the reversibility effect of denosumab as well as the rebound effect after discontinuation of denosumab leads to BMD loss and increases risk of multiple vertebral fractures, particularly in high-risk patients.

Based on current data, denosumab should not be discontinued without evaluating a different BTA in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

In these patients, the choice to continue with antiresorptive therapy might be suggested by common sense, due to the lack of strong evidence in the literature generating clear recommendations.

Statement 10.1 *In PCa patients on treatment with BPs or denosumab for CTIBL, after discontinuation of ADT, the fracture risk should be reassessed (using a validated algorithm for fracture risk, such as DeFRA, FRAX). If the patient experienced no fracture during treatment and has no other risk factors (BMD T-score > -2.5, obesity, age, sarcopenia, previous osteoporotic fractures, parent fractured hip, current smoking or alcohol, glucocorticoids, rheumatoid arthritis, secondary osteoporosis), BTAs can be discontinued, and bone health can continue to be monitored. If the patient presents any additional risk factor, monitoring and antiresorptive therapy with BPs or denosumab should be carried on.*

Level of consensus: 85% agree; 1.7% disagree; 13.3% uncertain

Statement 10.2 *For patients that experienced fragility fracture or a decline in BMD during BPs treatment could be switched to denosumab 60 mg/6 months.*

Level of consensus: 75% agree; 0% disagree; 25% uncertain

Statement 10.3 *A decision to discontinue denosumab could be made after discontinuation of ADT, but bone turnover rebound, and rapid bone loss must be monitored. Bisphosphonate (mainly Zoledronic acid, ZA) therapy should be considered, especially in high-risk patients, according to prescriptive rules.*

Level of consensus: 87.3% agree; 4.8% disagree; 7.9% uncertain

Statement 10.4 *Patients considered at high fracture risk could either continue denosumab therapy or be switched to BPs, in the absence of contraindications.*

Level of consensus: 83.3% agree; 3.3% disagree; 13.3% uncertain

Statement 10.5 *For patients who discontinue denosumab and experience rapid bone loss or new fracture despite bisphosphonate administration, retreatment with denosumab is likely to stop fracture risk and restore BMD by reducing bone turnover.*

Level of consensus: 61.7% agree; 0% disagree; 38.3% uncertain

Statement 10.6 *In patients who are not candidates for bisphosphonate therapy or who remain at high risk of fracture despite denosumab treatment, denosumab should be continued.*

Level of consensus: 75% agree; 0% disagree; 25% uncertain

11. How to improve bone health in nmHSPC patients?

In PCa early increase in fat body mass has recently been shown to predict a higher risk of skeletal-related events (SREs), a higher risk of death and a non-significant higher risk of disease recurrence. On the other hand, ADT-associated sarcopenic obesity further increases the risk of fragility fractures by increasing bone turnover, decreasing muscle mass, strength, and function. Furthermore, sarcopenic obesity is an independent indicator of poor prognosis.[26,35-39]

Statement 11.1 *All patients with nmHSPC should undergo to a total body composition by DEXA, in addition to weight detection and BMI , for lean body mass and fat mass assessment at baseline and during androgen deprivation treatment to reduce cardiovascular risk, sarcopenic obesity risk and improve bone health.*

Level of consensus: 81.7% agree; 3.3% disagree; 15% uncertain

Statement 11.2 *All patients with nmHSPC should undergo a nutritional assessment at baseline and during androgen deprivation treatment in order to reduce cardiovascular risk, sarcopenia risk and improve bone health.*

Level of consensus: 85% agree; 8.3% disagree; 6.7% uncertain

Statement 11.3 *Supervised clinical exercise programs should be included in clinical care programs for nmHSPC.*

Level of consensus: 93.3% agree; 0% disagree; 6.7% uncertain

b) *Metastatic hormone sensitive prostate cancer*

ADT with luteinising hormone-releasing hormone agonists or antagonists has been the treatment of choice in the mHSPC setting for decades, with an estimated median overall survival (OS) of about 3.5 years in contemporary series.[40,41] The addition of chemotherapy, new hormone therapies (NHT) and radiotherapy with ADT at the time of initiating systemic therapy for mHSPC has been shown to improve quality of life and OS.[42]

In the last decades several efforts have been made to guide the first line treatment for mHSPC, which should be chosen based on multiple factors, including drugs' tolerability profile, costs, duration of treatment and patients' clinical characteristics, such as disease volume or patients' risk.[42]

In the CHAARTED and STAMPEDE trials, combining treatment of docetaxel and ADT demonstrated an OS gain ranging from 10.4 to 16 months, respectively.[40,41] In the CHAARTED study, a prospective stratification of high- versus low-volume disease Docetaxel was found to significantly improve OS in patients with high-volume disease (defined as the presence visceral metastases and/or four or more bone lesions, with one or more beyond the pelvis and vertebral bodies) but not in those with low volume disease.[40] However, this contrasts with the benefit observed in the STAMPEDE trial, where the advantage in OS was observed regardless of disease volume.[41]

In the LATITUDE trial, the addition of abiraterone acetate to ADT was shown to improve OS of 6.8 months (53.3 vs 36.5 months) in high risk mHSPC patients (defined as the presence of at least two high-risk features, including ≥3 bone metastases, visceral metastases, and/or Gleason ≥8).[43] Adding abiraterone acetate and ADT improve OS of

33.6 months (79.2 vs 45.6 months) in the STAMPEDE trial, without interaction according to disease volume or patient's risk.[44,45]

Enzalutamide, apalutamide and darolutamide provided a significant OS benefit in patients with mHSPC enrolled in the ENZAMET (HR 0.67, 95% CI 0.52—0.86), TITAN trials (HR 0.67, 95% CI 0.51—0.89) and ARASENS trial (HR 0.68, 95% CI 0.57-0.80),[46-48] without any difference according to disease volume in the subgroups analyses.

A cross trials indirect comparison is inappropriate, given the different population and study design of these trials; however, in all these trials the OS advantage of combining ADT with chemotherapy and/or NHT was also associated with a significant benefit in the secondary end points and leads to support these strategies in clinical practice.

1. Among patients receiving systemic treatment for mHSPC, which are those at risk of fracture?

ADT represents a standard of care in the management of advanced PCa.[49] In men with PCa surviving at least 5 years after diagnosis, treatment with ADT is associated with a higher risk of osteoporotic fractures (19.4% vs 12.6%, p<0.001), and the fracture risk increased with the number of ADT doses administered.[8] Moreover, in mHSPC patients, results from ARCHES, ARASENS, TITAN, LATITUDE and STAMPEDE suggest that treatment with ADT + NHT was associated with a numerically higher non-pathological fracture rate (with no more than a 3 percentage-point difference), compared with ADT.[43,44,46,48] It is possible that a more prolonged period and a more potent inhibition of testosterone activity may enhance bone turnover and bone fragility.[50]

Despite the risk of bone fragility, the association of NHT to ADT has shown a significant benefit in bone outcomes such as median time to first SREs and symptomatic skeletal event—free survival.[43,44,46-48]

Statement 1 All patients receiving ADT +/- docetaxel +/- NHT should be treated with bone bone-targeting agents for fragility fracture prevention.

Level of consensus: 75.4% agree; 8.2% disagree; 16.4% uncertain

2. Are there other independent fracture risk factors to consider when deciding to use drugs for bone health in patients with mHSPC?

Statement 2 In mHSPC the independent factors of fracture risk (BMD, familiarity for fragility fractures, corticosteroid therapy with >5mg/prednisone equivalent in the past for more than 3 months consecutively or ongoing, metabolic bone diseases or fragilizing disease treatment, disability or high risk of fall, age, anamnesis for low-energy trauma fractures) should be evaluated before starting any antifracture prevention therapy. However, the fracture risk is independent of these factors that are, if present, additive in the risk estimation. Consequently, every patients candidate to treatment for mHSPC, should receive bone protective agents independently from the individual fracture risk.

Level of consensus: 78.7% agree; 9.8% disagree; 11.5% uncertain

3. In When antiresorptive therapy should be started in males given systemic treatment for mHSPC?

In the mHSPC setting the use of ZA 4 mg monthly or denosumab 120 mg monthly is not recommended because no study demonstrate the efficacy of denosumab or others BTAs in pathological SREs reduction. Several clinical trials in mHSPC have investigated ZA.

In particular, in men with mHSPC and bone metastases, early treatment with ZA in the CALGB 90202 study yielded no benefit in term of incidence reduction of SREs, compared with placebo, in terms of time to first SREs and OS.[51] In the same setting, no benefit regarding time to first SREs and OS was provided by ZA in the STAMPEDE and in the ZAPCA trials.[52,53] Recently, an analysis of routinely collected healthcare data from the STAMPEDE docetaxel.

and zoledronic acid comparisons have been presented with the aim to quantify fracture incidence in men with HSPC

recruited to the STAMPEDE (using routinely collected health care data through Hospital Episode Statistics) and to evaluate the impact of adding ZA (4 mg/every 3 weeks) or docetaxel on fracture risk. The 5-year cumulative incidence of fracture related hospitalisations was high in both nmHSPC (12%), and mHSPC (24%) patients treated with ADT. Docetaxel did not significantly alter the risk of fracture related hospitalisations in both nmHSPC and mHSPC patients. Zoledronic acid significantly reduced the risk of fracture related hospitalisations in mHSPC patients but not in nmHSPC ones.[54]

Statement 3 In mHSPC patients a therapy with antiresorptive drugs at the doses and schedule for SREs prevention should not be started.

Level of consensus: 80.3% agree; 4.9% disagree; 14.8% uncertain

4. In males in treatment for mHSPC , when should antiresorptive therapy be started and which drugs and schedules to be used for the prevention of CTIBL and the reduction of the risk of fracture?

All BTAs at all schedules and doses used were able to prevent bone loss and/or improve BMD compared with placebo. However, the only agent that demonstrated effective in reducing the incidence of new vertebral fractures is Denosumab.[7,13-16]

Vitamin D supplementation is part of the effect on BMD and fracture risk of BPs or denosumab. Furthermore, the lack of vitamin D supplementation impairs the positive effect on bone health outcome of bone modifying agents and exposes patients to the risk of hypocalcaemia, especially in the presence of osteoblastic bone metastasis.[17,55-57]

Statement 4.1 BTAs should be considered from the start of ADT itself for primary prevention of CTIBL.

Level of consensus: 75.4% agree; 4.9% disagree; 19.7% uncertain

Statement 4.2 In patients with mHSPC on ADT +/- chemotherapy +/-ARSI for the prevention of risk of fracture is advisable denosumab 60 mg/every 6 months. In case of

prescriptive ineligibility to therapy with denosumab and lack of reimbursement, the choice of another BTA (alendronate 70 mg/weekly, risedronate 35 mg/weekly or clodronate acid/weekly or zoledronate acid 4 mg every 6 months) might be a choice.

Level of consensus: 93.6% agree;3.2% disagree; 3.2% uncertain

Statement 4.3 Before starting and during any hormonal therapy, the levels of vitamin D ($\geq$30ng/mL) should be evaluated and normalized, regardless of the bone-modifying agent. A calcium intake of about 1000 mg/day or administration of calcium element at the equivalent dose and daily dose of Vitamin D 1500−2000IU, during antiresorptive therapy is mandatory.

Level of consensus: 90.2% agree; 3.3% disagree; 6.5% uncertain

5. **Patients with mHSPC on ADT+ docetaxel and/or NHT: how long should they be treated with antiresorptive drugs for the prevention of the risk of fractures?**

Statement 5 If no adverse events, anti-fracture treatment with BTAs should be continued until the diagnosis of castration resistance. After the diagnosis of castration resistance, BTAs should be administered at the same doses and schedule of mCRPC with bone metastases. If no bone metastases occur in mCRPC, the doses and schedule are the same of CTIBL prevention.

Level of consensus: 93.6% agree; 1.6% disagree; 4.8% uncertain

6. **How to diagnose and monitor the bone health in mHSPC during ADT and docetaxel and/or NHT?**

Statement 6 mHSPC patients should be monitored for metastatic disease by scintigraphy, CT scan or any other evaluation at physician's choice. Moreover, bone health monitoring should be performed in the same way as nmHSPC (Monitor: Vitamin D; serum calcium and PTH; DEXA scan with trabecular bone score, if available; if possible: Bone turnover markers; height, weight and BMI and body composition. In case of back pain or height loss perform a spine radiography).

Level of consensus: 83.6% agree; 3.3% disagree; 13.1% uncertain

7. **For patients who are already being treated for previous osteoporosis and who are candidates for ADT and docetaxel and/or NTH for mHSPC, which treatment is recommended?**

The degree of fracture risk and the underlying mechanisms of fragility fracture in postmenopausal and male osteoporosis are quite different from those found in androgen deprivation therapy. Fragility fracture in PCa patients in ADT occur independently of the levels of bone mass, probably due to an altered bone quality. BPs are effective in reducing the fracture risk in postmenopausal and male osteoporosis, through an increase in bone mass, but not in patients with mHSPC. Only denosumab at the same dosage has evidence to reduce the fracture risk in all setting of fragility.[25,58,59]

Statement 7.1 Patients should continue the same treatment for previous osteoporosis, as long as it involves calcium and vitamin D supplementation and BPs (alendronate 70 mg/weekly or clodronate acid/weekly or zoledronate acid/every 6 months) or denosumab 60 mg/ every 6 months.

Level of consensus: 88.5% agree; 3.3% disagree; 8.2% uncertain

Statement 7.2 Patients mHSPC in treatment with BPs for previous osteoporosis should be switched to denosumab 60 mg/ every 6 months for prevention of fragility fractures.

Level of consensus: 59% agree; 18% disagree; 23% uncertain

c) ***Non metastatic castration resistant prostate cancer***

PCa cells under the selective pressure of ADT develop adaptive mechanisms of survival that lead to castration-resistant disease through androgen receptor (AR) dependent (i.e. Amplifications, mutations, AR splice variants, intratumorally androgen synthesis and AR enhancer amplification, resulting in persisting AR activation) and AR-independent mechanisms.[60,61]

NmCRPC is a condition characterized by biochemical progression during ADT, despite castrate serum testosterone level < 2 ng/ml.

In the past years, the standard of care for nmCRPC patients was maximal androgen blockade (MAB), consisting of the addition of a first generation antiandrogen (i.e., bicalutamide) to ADT; this approach was associated to Prostate-Specific Antigen (PSA) response but no survival benefit was ever demonstrated.[62-64]

Apalutamide, darolutamide and enzalutamide are new-generation antiandrogens (ARSI) that not only competitively inhibit the AR ligand-binding domain, impair AR translocation to the nucleus and obstruct AR-mediated transcription.[65]

In men with nmCRPC with a PSA doubling time $\leq$ 10 months (high-risk nmCRPC), apalutamide, darolutamide and enzalutamide demonstrated advantage in preventing metastasis development compared with placebo.[66-68]

Basing on the achievement of the primary end point (metastasis free survival, MFS), secondary and point and the good safety-tolerability profile in the phase 3 registration trials (SPARTAN, PROSPER, ARAMIS),[66-68] the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) granted approval for apalutamide, enzalutamide and darolutamide in men with high-risk nmCRPC.

Despite the clinical benefit provided by ARSI, falls and non-pathological fractures represent a common adverse event during treatment with all drugs tested. The BONENZA study shows that after 18 months of enzalutamide, fat body mass increases by 22% and lean body mass decreases by 6%. The change is therefore twice as high as ADT alone. In these patients, ARSI-related bone turnover adds to the effect of ADT on bone fragility (loss of bone mass, qualitative/microarchitectural alterations and changes in body mass, as

already mentioned in HSPC setting). In fact, according to current prescriptive indications, primary prevention is indicated in men with PC at high risk of fracture due to ADT.

1. **Among patients with nmCRPC receiving ADT +/- ARSI, which are those at risk of fracture?**

Statement 1 All patients receiving ADT +/- ARSI should be treated with drugs with evidence of antifracture efficacy.
Level of consensus: 88.9% agree; 1.6% disagree; 9.5% uncertain

2. **In males affected by nmCRPC on ADT +/- ARSI, which are the drugs to be used for the reduction of the risk of fracture?**

Statement 2.1 Patients with nmHSPC treated for bone health and become nmCRPC, should continue treatment for bone health.
Level of consensus: 90.2% agree; 3.3% disagree; 6.5% uncertain

Statement 2.2 In patients with nmCRPC on ADT +/- ARSI for the prevention of risk of fracture denosumab 60 mg/every 6 months is advisable. In case of prescriptive ineligibility to therapy with denosumab and/or lack of reimbursement, the choice of another BTA (alendronate 70 mg/weekly, risedronate 35 mg/weekly or ZA 4 mg every 6 months) might be a choice.
Level of consensus: 87.4% agree; 6.3% disagree; 6.3% uncertain

Statement 2.3 Before starting and during any hormonal therapy, the levels of vitamin D ($\geq$30ng/mL) should be evaluated and normalized, regardless of the bone-modifying agent.
Level of consensus: 88.6% agree, 1.6% disagree, 9.8% uncertain

Statement 2.4 The administration of calcium and daily dose of Vitamin D 1500—2000IU, to reach and maintain the value between 30ng/ mL and 50 ng/ml(75nmol/L), during antiresorptive therapy is mandatory.
Level of consensus: 90.2 % agree; 0% disagree; 9.8% uncertain

Statement 2.5 The modalities for diagnosis and monitoring of bone health are the same for nmHSPC and nmCRPC disease.
Level of consensus: 93.4% agree; 0% disagree; 6.6% uncertain

Statement 2.6 Patients who has suboptimal response to BPs with incident fracture, declining BMD, or persistently low could be switched to denosumab 60 mg/every 6 months.
Level of consensus: 75.4% agree; 1.6% disagree; 23% uncertain

3. **Is it necessary to intensify treatment for bone health in high-risk nmCRPC patients receiving ADT and ARSI compared to low-risk nmCRPC patients receiving ADT alone?**

The role of denosumab for prevention of bone metastasis in men with nmCRPC was investigated in a large phase III

trial, in which 1432 patients were randomized to receive 120 mg denosumab or placebo every 4 weeks.[69] Bone-metastasis-free survival (bone-MFS), primary end point of the study, was improved of 4.2 months with denosumab (HR 0.85, 95% CI 0.73—0.98, p = 0.028). Denosumab also delayed time to first bone metastasis (HR 0.84, 95% CI 0.71—0.98, p = 0.032) and time to symptomatic bone metastasis (HR 0.67, 95% CI 0.49—0.92, p = 0.01). However, no OS benefit was observed. In this study, patients with aggressive PSA kinetics (PSA $\geq$ 8 µg/L within 3 months before randomization and/or PSA doubling time $\leq$ 10 months) showed a bone-MFS prolongation of 7.2 months compared to placebo (HR 0.77, 95% CI 0.64—0.93, p = 0.0064).

Nevertheless, FDA and EMA did not approve denosumab for the treatment of nmCRPC because of the lack of OS advantage and improvement in bone-MFS was considered not clinically relevant compared to the potential side effects.[70]

Statement 3 No different treatment for bone health is advisable in high risk and low risk nmCRPC.
Level of consensus: 84.1% agree; 1.6% disagree; 14.3% uncertain

4. **In high risk nmCRPC, can the choice of the type of ARSI be influenced by factors related to bone health?**

The results from SPARTAN and PROSPER suggest that treatment with apalutamide and enzalutamide further increases the fracture risk (the majority of adverse events were grade 1 or 2) in men with nmCRPC receiving long-term ADT. Nevertheless, darolutamide was not associated with a higher rates of falls or fractures than placebo and improved time to first symptomatic skeletal event despite few patients using osteoclast-targeted therapies.[66-68]

Statement 4 In high risk nmCRPCpatients considered at high fracture risk for obesity, age, sarcopenia or previous osteoporotic fractures, low bone mass, treatment with darolutamide should be preferred to enzalutamide or apalutamide basing on the results of the registration trials.
Level of consensus: 54.1% agree; 11.5% disagree; 34.4% uncertain

5. **In high-risk nmCRPC patients, can the choice of ARSI type influence bone health treatment?**

Statement 5 Patients receiving ARSI in combination with ADT for high-risk nmCRPC should receive bone health treatment regardless of the type of ARSI used, to reduce the incidence of non-pathological fractures.
Level of consensus: 83.6% agree; 8.2% disagree; 8.2% uncertain

6. **In high risk nmCRPC, can it be appropriate to carry out a fall risk assessment before deciding on the choice of the type of ARSI to be used?**

In the SPARTAN and PROSPER trials, apalutamide and enzalutamide reported a higher incidence of falls than placebo.[66,67] On the other hand, in the ARAMIS trial darolutamide shown an incidence of falls and fractures even

lower than placebo.[68] In particular, a higher incidence of fall (19.2% vs 7.2%) and fracture (15.8% vs 9.9%) was seen in patients aged ≥75 years compared to patients aged ≤ 74 years.[71] Both enzalutamide and apalutamide cross the blood-brain barrier (BBB) and can be considered for use in brain metastasis.[72] A study evaluating tissue distribution of BBB penetration in an animal model demonstrated that darolutamide has a 10-fold lower BBB penetration than enzalutamide with fewer central nervous system side effects, including falls.[73] There are multiple validated fall-risk assessment tools. For example, the Hendrich II Fall Risk Model and the 12-item Falls Risk Questionnaire are validated tool to estimate the risk of fall and for secondary prevention of falls.[74-76] An exploratory analysis of fall incidence from 5 placebo-controlled trials of denosumab, demonstrated that denosumab reduces fall incidence. This analysis included trials in women with postmenopausal osteoporosis and low bone mass, men with osteoporosis, women receiving adjuvant AIs for breast cancer, and men receiving ADT for PCa. The estimated risk of falls was lower with denosumab (HR 0.79; 95% confidence interval 0.66-0.93; p = 0.0061). Denosumab may reduce the risk of falls in addition to its established fracture risk reduction by reducing bone resorption and increasing bone mass.[77]

Statement 6.1 *Physicians should incorporate fall risk model and body composition by DEXA (for sarcopenia diagnosis)in clinical practice, especially in patients taking high-risk medications or patients with preexisting conditions who have a high risk of fall.*

Level of consensus: 82% agree, 1.6% disagree ; 16.4% uncertain

7. How long patients in ADT＋/- ARSI for nmCRPC should be treated with denosumab or BTAs for the prevention of the risk of fractures?

Statement 7 *Treatment with BPs or denosumab should be performed until the development of mCRPC, then shift to the doses and schedules of bone metastatic CRPC.*

Level of consensus: 78.7% agree; 1.6% disagree; 19.7% uncertain

8. Are there any safety concerns for long-term denosumab and BPs?

During the long-term treatment with BTAs in patients with PCa, the adverse effects of BTAs might increase because of both ageing and cumulative drug exposure. Clinical trial data on safety profile of BTAs cannot be extrapolated to longer treatment periods and cumulative drug exposure. However, 10-year data on fracture rates and bone safety assessments from the FREEDOM extension,[78] indicate that denosumab maintains a favorable efficacy and bone safety profile for 10 years of continuous treatment in in post-menopausal women. Atypical femoral fractures occurred in two women, one after 3 years and one after 7 years of treatment with denosumab, with no further cases in the last 3 years of the extension. By contrast, of the 13 cases of ONJ, 8 occurred during the first 5 years and 5 through years 8 to 10 of the extension treatment.[79-81]

Nevertheless, this possible association between duration of denosumab therapy and higher risk of ONJ remains to be confirmed.

Conversely, other studies did not find that the incidence of serious complications during prolonged treatment with BPs was higher than that of placebo during a follow-up of up to 72 months, confirming a previous long-term follow-up study (72 months).[82]

Statement 8 *BTAs maintain a favorable efficacy and bone safety profile during long-term treatment with a low absolute risk for serious complications.*

Level of consensus: 78.7% agree; 6.6% disagree; 14.7% uncertain

d) *Metastatic castration resistant prostate cancer*

In advanced PCa the most common site of metastatic disease is bone, especially axial skeleton, pelvis, and long bones. Multiple factors contribute to the bone tropism and reciprocal signaling between bone microenvironment cells (osteoblasts, osteoclasts and other cells) and PCa cells through the secretion of cytokines, growth factors and proteases promote PCa cell survival and growth in bone niches.[83-85] Pathologic fractures are directly related to metastatic lesions: up to 22% of men with mCRPC experience pathologic fractures during their disease due to weakened bone integrity in the area of metastasis. Treatment-related benign osteoporotic fractures occur due to the decline of BMD and the increased risk of osteoporosis. In addition to pathologic fractures, hypercalcemia, spinal cord compression, surgery to bone and radiotherapy to bone are the five events defined as SREs by FDA. SREs negatively correlate with survival: pathologic fractures and metastatic spinal cord compressions are associated with a significantly increased risk of death.[86]

To date, the treatment landscape for mCRPC patients includes chemotherapy (docetaxel and cabazitaxel), ARSI (enzalutamide and abiraterone), radiopharmaceutical therapy (radium-223 and [177]Lutetium-PSMA-617) and poly ADP-ribose polymerase inhibitors (PARPi) (Olaparib and rucaparib).[87-89]

Docetaxel became the standard of care as first-line therapy in mCRPC patients, since demonstrating improved OS (18.9 vs 16.5 months, HR 0.76; 95% CI 0.62−0.94, p=0.009) alone or with estramustine (17.5 months vs 15.6 months, HR 0.8; 95% CI 067−0.97, p=0.02) compared to mitoxantrone.[89,90]

Cabazitaxel was demonstrated to improve OS compared with mitoxantrone in mCRPC patients progressing on or after docetaxel (15.1 vs 12.7 months, HR 0.7; 95% CI 0.59−0.83, p <0.0001).[85] Abiraterone and enzalutamide, two NHTs, demonstrated to be superior to placebo in terms of OS in mCRPC patients post docetaxel and, subsequently, also in docetaxel naive patients.[72,91-93]

In the ALSYMPCA trial, radium-223 reduced the risk of death by 30% (HR 0.7; 95% CI 0.58−0.83; p<0.001) and prolonged the time to the first symptomatic SREs (secondary end point; HR 0.66; 95% CI, 0.52 to 0.83; P<0.001), compared to placebo in symptomatic mCRPC patients with

bone metastases post- docetaxel, or in patients ineligibleor refused to receive docetaxel.[94] After the result of the ERA 223 trial, radium-223 use is restricted by EMA for patients who have previously received docetaxel and an ARSI.[95,96] In this trial, the combination of radium-223 and abiraterone showed an increased incidence of fractures (29% vs 11%) and a numerical reduction in median OS (30.7 versus 33.3 months; p = 0.13) compared to abiraterone alone.[95]

Recently, [177]Lutetium-PSMA-617 demonstrated to improve OS in PSMA-positive mCRPC patients previously treated with at least one ARSI and one or two taxane regimens compared to standard care alone (15.3 vs 11.3 months, HR 0.62; 95% CI 0.52−0.74; p <0.001).[87] The protocol permitted standard of care consisting of BPs, radiotherapy, denosumab, corticosteroid or ARSI.[87] In the same trial, the median time to the first symptomatic skeletal event or death was 11.5 months in the ^{177}Lu-PSMA-617 group, as compared with 6.8 months in the control group (HR 0.50; 95% CI, 0.40 to 0.62; P<0.001).[87]

In mCRPC patients with alteration in Breast Cancer gene (BRCA) 1, BRCA2, or ATM, Olaparib was found to reduce the risk of death by 31% enzalutamide or abiraterone pretreated patients; this result lead to EMA approval of Olaparib for BRCA1 and BRCA2 mutated mCRPC patients.[97]

1. Among patients in treatment for mCRPC, which are those at risk of pathological and fragility fracture?

The available data demonstrate that patients with mCRPC may benefit from the use of NHT as for progression delay, pain control and QoL improvement. There is no direct comparison between abiraterone and enzalutamide and data from a meta-analysis of registration trials demonstrated no significant difference in terms of radiological progression free survival (rPFS) and time to first SREs (tSRE).[98]

Therefore, a retrospective real-world study reported abiraterone acetate was associated with better SREs outcomes than enzalutamide (hazard of SREs 0.34 (95% 1.34 CI 1.06 to 1.69); p=0.015).[99]

Despite the clinical benefit provided by NHT, the rate of non-pathological fractures was higher on NHT, compared with placebo, also in men with mCRPC in both pre-chemotherapy and post-chemotherapy settings.

Statement 1.1 All patients with mCRPC and bone metastases should be treated with bone protecting agents with the aim to SREs reduction as well as to prevent CTIBL and, consequently, the risk of fragility fractures.

Level of consensus: 93.6% agree; 1.6% disagree; 4.8% uncertain

Statement 1.2 All patients affected by mCRPC without bone metastases should be treated with bone protecting agents with the aim to reduce CITBL and, consequently, the risk of fragility fractures.

Level of consensus: 83.9% agree; 6.4% disagree; 9.7% uncertain

Statement 1.3 In patients with mCRPC without bone metastases, bone health should be treated, assessed, and monitored as in nmCRPC patients.

Level of consensus: 92% agree; 0% disagree; 8% uncertain

2. In males affected by mCRPC, which drugs should be used for the reduction of the risk of SREs and for the prevention of CTIBL fragility fracture?

All patients with mCRPC should be treated with supportive treatment to preserve bone health, taking into consideration that the effects on bone fragility and SREs prevention depend on the dose and schedule given. BPs and denosumab improve bone outcomes in patients with mCRPC. Moreover, the concomitant use of BTAs demonstrated to further increase the clinical benefit of abiraterone and prednisone in terms OS, time to Eastern Cooperative Oncology Group(ECOG) deterioration and time to opiate use for cancer-related pain in mCRPC chemotherapy naïve patients.[100] ZA is the first-generation bisphosphonate enabling to reduce the incidence of SREs and prolong the median time to the first SREs onset in mCRPC with bone metastases. In particular, it was reported that ZA administered every three weeks prolonged the median time to the first onset of SREs by 167 days compared with a placebo.

In patients with mCRPC with bone metastases, ZA improved progression free survival (PFS), skeletal pain and SREs only in men with a Gleason score ≥8. Denosumab was better than ZA for prevention of skeletal-related events: it proved to be superior to ZA in delaying occurrence of the first SREs.[101,102]

Statement 2.1 Denosumab (120 mg/ every 4 weeks) should be used in patients with mCRPC as it may delay the onset of SREs.

Level of consensus: 92% agree; 3.2% disagree; 4.8% uncertain

Statement 2.2 ZA is considered the bisphosphonate of choice in patients with mCRCP as it may delay the onset of SREs. ZA at a dosage of 4 mg every 4 weeks is considered the standard, whilst higher doses are not recommended.

Level of consensus: 91.9% agree; 3.2% disagree; 4.8% uncertain

Statement 2.3 Vitamin D and calcium supplementation is mandatory during treatment with BTAs. The administration of calcium and daily dose of Vitamin D 1500-2000IU after a load dose (5000 UI/day for 30 days), to reach and maintain the value between of 30ng-50 ng/ mL (75nmol/L), during antiresorptive therapy is mandatory.

Level of consensus: 95.2% agree; 1.6% disagree; 3.2% uncertain

3. Who should be treated with denosumab and who should be treated with ZA?

Real world data reveal that denosumab is used more frequently than ZA in studies including mCRPC with bone metastases.[17,50,72,87-98,100-107] The choice between the two treatment should consider patient's characteristics.

In particular, about 50% of cancer patients suffer from renal failure; the risk of worsening renal function should be considered before initiating BTAs. BTAs cause increased risk of hypocalcemia, especially in patients with renal

impairment by inhibiting bone resorption, inducing a positive shift in bone balance with secondary hyperparathyroidism if patients are no vitamin D repleted. The risk of hypocalcemia is related to potency of bone resorption activity. Denosumab is the more potent bone resorption inhibitor and in patients with reduced renal function and inadequate vitamin D remodulation has a higher risk of hypocalcemia.[16,108]

Statement 3.1 *The physician's choice between ZA and denosumab should consider comorbidities (i.e. renal impairment) and patient characteristics (i.e. easy vascular access, home therapy).*

Level of consensus: 100% agree; 0% disagree; 0% uncertain

Statement 3.2 *Denosumab might be considered the preferred option in mCRPC patients with bone metastases according to the demonstration of reduction in SREs. However, the choice between denosumab and ZA could be based on many factors: direct costs (drug price for healthcare system), indirect costs (commitment of healthcare structures), individual risk of side effects (renal toxicity, ONJ, hypocalcemia), preferences of the patient.*

Level of consensus: 84.1% agree; 6.4% disagree; 9.5% uncertain

4. When should BTAs be started in patients with mCRPC?

Real-world data reveal that BTAs are not adequately administered in patients with mCRPC and bone metastases. A recent study reported that 26% of patients with bone metastases did not receive a BTA, and only 53% received treatment within 3 months of bone metastasis diagnosis.[109] A retrospective analysis reported that 34% of mCRPC. patients did not use bone health agents at any time.[105]

Statement 4.1 *In mCRPC patients, bone protecting agents should be started at the dose and schedule for SREs prevention at the time of the first metastasis diagnosis, even if already used to prevent CTIBL, in order to reduce incidence of SREs.*

Level of consensus: 88.7% agree; 4.8% disagree; 6.5% uncertain

Statement 4.2 *Greater awareness of physicians about the importance of BTAs is needed to improve their use in patients with mCRPC and bone metastases.*

Level of consensus: 98.4% agree; 0% disagree; 1.6% uncertain

5. How long should be treated with BTAs?

It is well known that the antiresorptive effect of BPs persist after stopping treatment for months or years (in osteoporosis patients) due to their high affinity for binding hydroxyapatite.

Denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation and its discontinuation may lead to an increased risk of multiple vertebral fractures in osteoporosis patients. Data from phase II and III clinical trials describe a rapid decrease of BMD as well as an increase in bone turnover markers after discontinuation of denosumab. Multiple vertebral fractures

were observed after discontinuation of denosumab because of a rebound increase in bone resorption, as suggested, but not proved, by a renewed analysis of FREEDOM and FREEDOM extension trial in postmenopausal women with osteoporosis.[31]

In breast cancer patients, the phase III ZOOM trial evaluated the efficacy of ZA administration every 4 weeks compared to ZA every 12 weeks, randomization occurring after completion of 12-15 months of monthly ZA. No differences in reduction in SREs and adverse events were observed, however N-terminal telopeptide increases over time more in patients receiving ZA every 12 weeks.[110]

Patients with bone metastases from breast or mCRPC(160 breast cancer, 103 CRPC), who were going to start or were already receiving BTAs, were randomized to 4- or 12-weekly ZA (24.0%) or denosumab (56.3%), or pamidronate (19.8%) for 2 years. After 2 years, the cumulative incidence rate of SREs was 32.7% (24.6% to 41.1%) and 28.1% (20.3% to 36.4%) for the 4- and 12-weekly intervention groups respectively. The HR for time to first SREs was 0.96 (95% CI = 0.63-1.47).[111]

Statement 5.1 *In mCRPC after 12-15 months of treatment with ZA every 4 weeks, the shift to a 12-weeks schedule of ZA could be considered, previous evaluations of risk/benefit ratio for the single patient (i.e., burden of bone metastases, systemic disease control).*

Level of consensus: 80.6%agree; 0% disagree; 19.4% uncertain

Statement 5.2 *Treatment with denosumab should be continued throughout the course of the disease because its stop may expose to pathological and fragility fracture risk. After denosumab discontinuation, shift to ZA every 4 or every 12 weeks can be considered.*

Level of consensus: 77.8% agree; 9.5.% disagree; 12.7% uncertain

6. The switch from ZA to denosumab: when and how to do it?

Switch from ZA to denosumab is sometimes necessary in patients who develop renal failure or progression of bone metastases. In a randomized phase II trial of denosumab in patients with bone metastases from PCa, breast cancer, or other neoplasms with elevated urinary N-telopeptide of type I collagen, or uNTX, despite ongoing intravenous BPS therapy, denosumab normalized uNTx levels more frequently than the continuation of IV BPs. Fewer patients receiving denosumab experienced on-study SREs than those receiving intravenous BPs.[112]

In a retrospective study, switching from ZA to denosumab resulted in a higher risk of ONJ than patients who did not switch. Even if it is known that the risk of ONJ increases with duration of exposure to BTAs, there are no definitive data for this. In addition, the switch may be necessary to allow continuation of recalcifying treatment in patients who develop renal impairment.[113]

Statement 6.1 *Switch from ZA to denosumab should be considered in patients who develop renal failure during ZA*

treatment or in patients who experienced a new SRE during ZA.

Level of consensus: 82.3% agree; 1.6% disagree; 16.1% uncertain

Statement 6.2 *Switch from ZA to denosumab can be performed after 4 weeks from the last ZA administration without adding adverse events, except for ONJ risk due to prolonged BTAs exposure. For this reason a close attention to oral cavity monitoring should be taken.*

Level of consensus: 92% agree; 3.2% disagree; 4.8% uncertain

7. Should ZA or denosumab therapy be used to reduce bone pain?

In three studies evaluating the analgesic effect of biphosphates, the administration of BPs did not lead to an analgesic effect compared to placebo.[114-116] Furthermore, 4 studies evaluated the consumption of analgesic drugs: BPs administration was not associated to a better control pain compared to placebo.[117]

A randomized trial demonstrated a benefit of ZA compared to placebo on pain, measured by the Brief Pain Inventory score (BFI), in terms of reduction of BFI in the first 12 weeks and no increase during the subsequent weeks.[118]

In the comparing trial of ZA and denosumab, pain, defined as adverse event, was not differently controlled in the two groups.[101]

Statement 7 *BPs and denosumab should be prescribed for the prevention of SREs, but an adequate treatment for pain should be added because the administration of BTAs did not demonstrate an analgesic effect compared to placebo.*

Level of consensus: 87.1% agree; 4.8% disagree; 8.1% uncertain

8. Radiometabolic therapies in mCRPC patients: why and how to pay attention to bone health?

Radium-223, as a cationic calcium-mimic, is absorbed and concentrated in the bone and binds to hydroxyapatite. Radium-223 deposits mostly in active bone remodeling areas such as osteoblastic bone metastasis and emits α-particles leading to cell death.[94] In the ERA-223 trial, patients with CT-naive asymptomatic or paucisymptomatic mCRPC on abiraterone acetate plus prednisone/prednisolone and randomized to receive radium-223 or placebo, the use of BTAs (ZA or denosumab) halved the number of patients with osteoporotic fractures in both arms (from 37% in the radium-223 arm and 15% in the placebo arm without BTAs, to 15% and 7%, respectively, with BTAs).[95] Similarly, in the EORTC 1333/PEACE III the association of enzalutamide and radium 223 compared to enzalutamide alone lead to a cumulative 1-year risk of fracture of 37.4% and 12.4%, respectively, without BTAs, and 0% in both arms with BTAs.[119] After the results of the ERA 223 trial, EMA reserved the use of radium-223 for patients who have had at least two previous treatments for PCa that has spread to the bone, or who cannot receive other treatments.

In contrast with radium-223, median time to first SREs was delayed in patients treated with Lu-PSMA.[87]

Statement 8.1 *Before, during, and after treatment with radium-223 bone health should be monitored. Radium-223 may be interrupted or stopped if fragility fractures are occurred.*

Level of consensus: 82.3% agree; 3.2% disagree; 14.5% uncertain

Statement 8.2 *Before starting and during treatment with radium-223, BTAs (denosumab 120 mg or ZA every 14 weeks) should be administered to protect bone from pathological and fragility fractures.*

Level of consensus: 87.1% agree; 0% disagree; 12.9% uncertain

9. How to diagnose and monitor the bone health in mCRPC?

Statement 9 *Monitor metastases by scintigraphy, NMR or any other evaluation at physician's discretion and monitor bone health by assessing the fracture risk as in non-metastatic disease (Monitor: vitamin D; serum calcium and PTH; DEXA scan with trabecular bone score, if available; if possible: bone turnover markers; height, weight, BMI and body composition. In case of back pain or height loss perform a spine radiography). Closer attention should be pay to vitamin D, serum calcium and PTH serum levels because of the higher risk of hypocalcemia during administration of ZA or denosumab at the dose for SREs prevention.*

Level of consensus: 96.8% agree; 1.6% disagree; 1.6% uncertain

10. In mCRPC patients treated with antiresorptive drugs (BPs, denosumab) for SREs prevention an oral cavity assessment is recommended before starting therapy, in order to reduce the risk of subsequent MRONJ?

The time range of onset of the BPs-associated ONJ is within 2 years; this interval tends to increase in patients on oral BPs therapy (typically after 3 years with a mean of 4.6 years).[120] For denosumab, data are mixed. According to some authors, the cumulative dose and duration of treatment do not influence the risk of developing drug-related ONJ as cases of disease have been described after a single administration of the drug.[121]

According to other authors, patients taking denosumab for a prolonged period appear to be at greater risk of developing ONJ.[122,123] This risk would further increase, resulting in faster onset of ONJ, in case of therapeutic switch from BPs to denosumab.[124]

Statement 10 *Before starting treatment with BPs or denosumab with schedule for SREs prevention adequately informed patients have to perform a dental visit to evaluate their oral health, to set up an adequate prevention program and possibly treat local pathologies before starting BTA therapy.*

Level of consensus: 100 % agree; 0% disagree; 0% uncertain

11. How to manage any dental procedures that may be necessary during anti-resorptive treatments for bone metastases in mCRPC?

The cumulative risk of ONJ in patients receiving BTAs increases with the time and reflects the rate of bone turnover suppression that largely depends on the dosage regimen and the duration of treatment.[30] In cancer patients with bone metastases, suspension of antiresorptive drugs must be considering a balance between a possible positive drug effect (in terms of reduction in the risk of SREs) and a potentially higher risk of a side effect anyway present (higher risk of ONJ namely triggered by alveolar surgery). In cancer patients on BTAs for bone metastases, the moment along the patient cancer history and along the drug administration history could influence this risk: in the first months of drug administration the suspension is potentially more harmful for the risk of SREs and less dangerous for the risk of triggering ONJ; on the other hand, in a patient treated for two years with BTAs, their suspension led to a benefit in terms of reduction in the risk of MRONJ without significantly enhancing the risk of SREs (anyway present).

Furthermore, this balance depends by the characteristics of the BTAs administered: denosumab is a monoclonal human anti-RANKL inhibitor with short half-life and without bone accumulation. Its suspension could lead to a possible rebound effect on the bone turnover, so that some authors advised against long suspensions. BPs have a long half-life and a possible antiangiogenic effect and are able to accumulate in the bone tissue, potentially influencing the post-extractive bone and soft tissue repair process. Although there are no univocal data on the efficacy of ZA suspension to reduce the risk of "post-extraction" ONJ, precautionary and temporary suspension has been claimed by most of authors as potentially useful.[27]

Statement 11.1 *Plan an assessment by the prescriber (high risk versus low risk of SREs) and by the dentist (high risk versus low risk of post-extraction complications) to determine the need for a precautionary suspension of ZA or denosumab before and after the dental procedure.*

Level of consensus: 93.5% agree; 0% disagree; 6.5% uncertain

Statement 11.2 *No definitive data have been published and, especially with ZA, there is not a safe timing for invasive oral/dental procedures due to its mechanism of action. If procedure is urgent, a suspension frequently applied of ZA or denosumab consists of a period of 4 weeks, at least, from the last assumption before any elective invasive oral or dental procedures. BTAs re-assumption should occur not before 6 weeks and only after a complete healing assessed by dentist.*

Level of consensus: 87.3% agree; 3.2% disagree; 9.5% uncertain

REFERENCES

1. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol*. 2002:2361-7; discussion 2367. vol. 6.

2. Greenspan SL, Wagner J, Nelson JB, Perera S, Britton C, Resnick NM. Vertebral fractures and trabecular microstructure in men with prostate cancer on androgen deprivation therapy. *J Bone Miner Res*. Feb 2013;28(2):325-332.

3. Boivin G, Meunier PJ. Changes in bone remodeling rate influence the degree of mineralization of bone. *Connect Tissue Res*. 2002;43(2-3):535-537. https://doi.org/10.1080/03008200290000934.

4. Wallander M, Axelsson KF, Lundh D, Lorentzon M. Patients with prostate cancer and androgen deprivation therapy have increased risk of fractures-a study from the fractures and fall injuries in the elderly cohort (FRAILCO). *Osteoporos Int*. Jan 2019;30(1):115-125.

5. Alibhai SM, Mohamedali HZ, Gulamhusein H, et al. Changes in bone mineral density in men starting androgen deprivation therapy and the protective role of vitamin D. *Osteoporos Int*. Oct 2013;24(10):2571-2579. https://doi.org/10.1007/s00198-013-2343-4.

6. Alibhai SM, Duong-Hua M, Cheung AM, et al. Fracture types and risk factors in men with prostate cancer on androgen deprivation therapy: a matched cohort study of 19,079 men. *J Urol*. 2010 American Urological Association Education and Research, Inc. Published by Elsevier Inc; 2010:918-23. vol. 3.

7. Smith MR, Egerdie B, Hernández Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. Aug 20 2009;361(8):745-755.

8. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005 Massachusetts Medical Society. 2005:154-64. vol. 2.

9. Morote J, Orsola A, Abascal JM, et al. Bone mineral density changes in patients with prostate cancer during the first 2 years of androgen suppression. *J Urol*. 2006:1679-83; discussion 1683. vol. 5.

10. Body JJ, Bergmann P, Boonen S, et al. Management of cancer treatment-induced bone loss in early breast and prostate cancer – a consensus paper of the Belgian Bone Club. *Osteoporos Int*. Nov 2007;18(11):1439-1450. https://doi.org/10.1007/s00198-007-0439-4.

11. Sullivan S, Wagner J, Resnick NM, Nelson J, Perera SK, Greenspan SL. Vertebral fractures and the misclassification of osteoporosis in men with prostate cancer. *J Clin Densitom*. Jul-Sep 2011;14(3):348-353.

12. Greenspan SL, Nelson JB, Trump DL, et al. Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. *J Clin Oncol*. Sep 20 2008;26(27):4426-4434.

13. Poon Y, Pechlivanoglou P, Alibhai SMH, et al. Systematic review and network meta-analysis on the relative efficacy of osteoporotic medications: men with prostate cancer on continuous androgen-deprivation therapy to reduce risk of fragility fractures. *BJU Int*. Jan 2018;121(1):17-28. https://doi.org/10.1111/bju.14015.

14. Kozyrakis D, Paridis D, Perikleous S, Malizos K, Zarkadas A, Tsagkalis A. The Current Role of Osteoclast Inhibitors in Patients with Prostate Cancer. *Adv Urol*. 2018;2018:1525832.

15. Alibhai SMH, Zukotynski K, Walker-Dilks C. Bone Health and Bone-Targeted Therapies for Nonmetastatic Prostate Cancer. *Ann Intern Med*. 2018:459-460. vol. 6.

16. Jakob T, Tesfamariam YM, Macherey S, et al. Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a network meta-analysis. *Cochrane Database Syst Rev*. Dec 3 2020;12(12):CD013020.

17. Bertoldo F, Cianferotti L, Di Monaco M, et al. Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). *Nutrients*. Oct 6 2022;14(19).

18. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*. Apr 4 2013;368(14):1314-1325.

19. Hershman DL, Unger JM, Wright JD, et al. Adverse Health Events Following Intermittent and Continuous Androgen Deprivation in Patients With Metastatic Prostate Cancer. *JAMA Oncol*. Apr 2016;2(4):453-461.

20. Briot K, Paccou J, Beuzeboc P, et al. French recommendations for osteoporosis prevention and treatment in patients with prostate cancer treated by androgen deprivation. *Joint Bone Spine*. © 2018. 2018. Published by Elsevier Masson SAS.; 2019:21-28. vol. 1.

21. Graham J, Kirkbride P, Cann K, Hasler E, Prettyjohns M. Prostate cancer: summary of updated NICE guidance. *BMJ*. 2014:f7524.

22. Saylor PJ, Kaufman DS, Michaelson MD, Lee RJ, Smith MR. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. *J Urol*. Jun 2010;183(6):2200-2205.

23. WHO Scientific Group Technical Report. Available at https://www.sheffield.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf. Accessed July 20, 2023.

24. Linee guida "Diagnosi, stratificazione del rischio e continuità assistenziale delle Fratture da Fragilità". Available at https://www.iss.it/documents/20126/8331678/LG-392_Fratture-da-Fragilit%C3%A0_v3.pdf/4e697d88-35ea-3130-b2e7-60cad527c10d?t=1677495524202. Accessed July 20, 2023.

25. Mazziotti G, Vena W, Pedersini R, et al. Prediction of vertebral fractures in cancer patients undergoing hormone deprivation therapies: Reliability of who fracture risk assessment tool (frax) and bone mineral density in real-life clinical practice. *J Bone Oncol*. Apr 2022;33:100421.

26. Palumbo C, Dalla Volta A, Zamboni S, et al. Effect of Degarelix Administration on Bone Health in Prostate Cancer Patients Without Bone Metastases. The Blade Study. *J Clin Endocrinol Metab*. © The Author(s) 2022. Published by Oxford University Press on behalf of the Endocrine Society For permissions, please e-mail: journals.permissions@oup.com.; 2022:3398-3407. vol. 12.

27. Campisi G, Mauceri R, Bertoldo F, et al. Medication-Related Osteonecrosis of Jaws (MRONJ) Prevention and Diagnosis: Italian Consensus Update 2020. *Int J Environ Res Public Health*. Aug 18 2020;17(16).

28. Watts NB, Grbic JT, Binkley N, et al. Invasive Oral Procedures and Events in Postmenopausal Women With Osteoporosis Treated With Denosumab for Up to 10 Years. *J Clin Endocrinol Metab*. © 2019 Endocrine Society.; 2019:2443-2452. vol. 6.

29. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009 Massachusetts Medical Society; 2009:756-65. vol. 8.

30. Campisi G, Mauceri R, Bertoldo F, Fusco V, Bedogni A. A pragmatic window of opportunity to minimise the risk of MRONJ development in individuals with osteoporosis on Denosumab therapy: a hypothesis. *Head Face Med*. Jul 9 2021;17(1):25.

31. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone*. © 2017 Elsevier Inc; 2017:11-17.

32. Tsourdi E, Zillikens MC, Meier C, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. *J Clin Endocrinol Metab*. © The Author(s) 2020. Published by Oxford University Press on behalf of the Endocrine Society For permissions, please e-mail: journals.permissions@oup.com; 2020.

33. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol*. 2008:45-53. vol. 1.

34. Koopal C, Janssen-Heijnen ML, van de Wouw AJ, van den Bergh JP. Fracture incidence in pre- and postmenopausal women after

completion of adjuvant hormonal therapy for breast cancer. *Breast*. © 2014 Elsevier Ltd; 2015:153-8. vol. 2.

35. Zheng R, Byberg L, Larsson SC, Höijer J, Baron JA, Michaëlsson K. Prior loss of body mass index, low body mass index, and central obesity independently contribute to higher rates of fractures in elderly women and men. *J Bone Miner Res*. Jul 2021;36(7):1288-1299. https://doi.org/10.1002/jbmr.4298.

36. Ali D, Tencerova M, Figeac F, Kassem M, Jafari A. The pathophysiology of osteoporosis in obesity and type 2 diabetes in aging women and men: The mechanisms and roles of increased bone marrow adiposity. *Front Endocrinol (Lausanne)*. 2022;13:981487.

37. Ohtaka A, Aoki H, Nagata M, et al. Sarcopenia is a poor prognostic factor of castration-resistant prostate cancer treated with docetaxel therapy. *Prostate Int*. Mar 2019;7(1):9-14.

38. Stangl-Kremser J, Mari A, Lai LY, et al. Sarcopenic Obesity and its Prognostic Impact on Urological Cancers: A Systematic Review. *J Urol*. Oct 2021;206(4):854-865. https://doi.org/10.1097/ju.0000000000001873.

39. Buttigliero C, Vana F, Bertaglia V, et al. The fat body mass increase after adjuvant androgen deprivation therapy is predictive of prostate cancer outcome. *Endocrine*. Sep 2015;50(1):223-230. https://doi.org/10.1007/s12020-015-0525-x.

40. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. *J Clin Oncol*. Apr 10 2018;36(11):1080-1087.

41. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol*. Dec 1 2019;30(12):1992-2003.

42. Cattrini C, Castro E, Lozano R, et al. Current Treatment Options for Metastatic Hormone-Sensitive Prostate Cancer. *Cancers (Basel)*. Sep 12 2019;11(9).

43. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. © 2019 Elsevier Ltd; 2019:686-700. vol. 5.

44. James ND, Clarke NW, Cook A, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). *Int J Cancer*. Aug 1 2022;151(3):422-434.

45. Hoyle AP, Ali A, James ND, et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. *Eur Urol*. © 2019. Published by Elsevier B.V.; 2019:719-728. vol. 6.

46. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med*. Jul 11 2019;381(2):121-131. https://doi.org/10.1056/NEJMoa1903835.

47. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med*. Jul 4 2019;381(1):13-24. https://doi.org/10.1056/NEJMoa1903307.

48. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *N Engl J Med*. Mar 24 2022;386(12):1132-1142.

49. Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015:v69-v77.

50. Santini D, Berruti A, Di Maio M, et al. Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion. *ESMO Open*. Mar 2020;5(2).

51. Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol*. Apr 10 2014;32(11):1143-1150.

52. Kamba T, Kamoto T, Maruo S, et al. A phase III multicenter, randomized, controlled study of combined androgen blockade with versus without zoledronic acid in prostate cancer patients with metastatic bone disease: results of the ZAPCA trial. *Int J Clin Oncol*. 2017:166-173. vol. 1.

53. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. Mar 19 2016;387(10024):1163-1177.

54. Jones C, Dutey-Magni P, Murphy LR, et al. 1768MO Incidence of fracture related hospitalisations in men with de novo high risk localised and metastatic hormone sensitive prostate cancer: Analysis of routinely collected healthcare data from the STAMPEDE docetaxel and zoledronic acid comparisons. *Annals of Oncology*. 2023;34:S956-S957. https://doi.org/10.1016/j.annonc.2023.09.2718.

55. Jacobs ET, Kohler LN, Kunihiro AG, Jurutka PW. Vitamin D and Colorectal, Breast, and Prostate Cancers: A Review of the Epidemiological Evidence. *J Cancer*. 2016;7(3):232-240.

56. Schwartz GG. Vitamin D in blood and risk of prostate cancer: lessons from the Selenium and Vitamin E Cancer Prevention Trial and the Prostate Cancer Prevention Trial. *Cancer Epidemiol Biomarkers Prev*.©2014 American Association for Cancer Research.; 2014:1447-9. vol. 8.

57. Lau LH, Cliff ERS, Wong V, et al. Hypocalcaemia following denosumab in prostate cancer: A clinical review. *Clin Endocrinol (Oxf)*. Jun 2020;92(6):495-502. https://doi.org/10.1111/cen.14169.

58. Cianferotti L, Bertoldo F, Carini M, et al. The prevention of fragility fractures in patients with non-metastatic prostate cancer: a position statement by the international osteoporosis foundation. *Oncotarget*. Sep 26 2017;8(43):75646-75663.

59. Nicolopoulos K, Moshi MR, Stringer D, Ma N, Jenal M, Vreugdenburg T. The clinical effectiveness of denosumab (Prolia®) in patients with hormone-sensitive cancer receiving endocrine therapy, compared to bisphosphonates, selective estrogen receptor modulators (SERM), and placebo: a systematic review and network meta-analysis. *Arch Osteoporos*. © 2023. International Osteoporosis Foundation and Bone Health and Osteoporosis Foundation.; 2023:18. vol. 1.

60. Galletti G, Leach BI, Lam L, Tagawa ST. Mechanisms of resistance to systemic therapy in metastatic castration-resistant prostate cancer. *Cancer Treat Rev*. © 2017 Elsevier Ltd; 2017:16-27.

61. Cattrini C, Zanardi E, Vallome G, et al. Targeting androgen-independent pathways: new chances for patients with prostate cancer? *Crit Rev Oncol Hematol*. © 2017 Elsevier B.V; 2017:42-53.

62. Sartor AO, Tangen CM, Hussain MH, et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer*. Jun 2008;112(11):2393-2400.

63. Lodde M, Lacombe L, Fradet Y. Salvage therapy with bicalutamide 150 mg in nonmetastatic castration-resistant prostate cancer. *Urology*. © 2010 Elsevier Inc; 2010:1189-1193. vol. 5.

64. Suzuki H, Okihara K, Miyake H, et al. Alternative nonsteroidal antiandrogen therapy for advanced prostate cancer that relapsed after initial maximum androgen blockade. *J Urol*. 2008:921-927. vol. 3.

65. Crawford ED, Schellhammer PF, McLeod DG, et al. Androgen Receptor Targeted Treatments of Prostate Cancer: 35 Years of Progress with Antiandrogens. *J Urol*. © 2018 American Urological Association Education and Research Inc. Published by Elsevier Inc; 2018:956-966. vol. 5.

66. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*. Apr 12 2018;378(15):1408-1418. https://doi.org/10.1056/NEJMoa1715546.

67. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Non-metastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. Jun 28 2018;378(26):2465-2474.

68. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. Mar 28 2019;380(13):1235-1246. https://doi.org/10.1056/NEJMoa1815671.

69. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. Jan 7 2012;379(9810):39-46.

70. FDA Panel Rejects Denosumab Against Bone Metastasis in Prostate Cancer. Available at https://www.mdedge.com/endocrinology/article/47400/oncology/fda-panel-rejects-denosumab-against-bone-metastasis-prostate. Accessed July 14, 2023.

71. Graff JN, Baciarello G, Armstrong AJ, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol*. © The Author 2015. Published by Oxford University Press on behalf of the European Society for Medical Oncology For permissions, please email: journals.permissions@oup.com; 2016:286-294. vol. 2.

72. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. Sep 27 2012;367(13):1187-1197. https://doi.org/10.1056/NEJMoa1207506.

73. Zurth C, Sandman S, Trummel D, Seidel D, Nubbemeyer R, Gieschen H. Higher blood—brain barrier penetration of [14 C]apalutamide and [14 C]enzalutamide compared to [14 C]darolutamide in rats using whole-body autoradiography. *Journal of Clinical Oncology*. 2019;37:156-156. https://doi.org/10.1200/JCO.2019.37.7_suppl.156.

74. Hendrich A, Nyhuis A, Kippenbrock T, Soja ME. Hospital falls: development of a predictive model for clinical practice. *Appl Nurs Res*. 1995:129-139. vol. 3.

75. Hendrich AL, Bender PS, Nyhuis A. Validation of the Hendrich II Fall Risk Model: a large concurrent case/control study of hospitalized patients. *Appl Nurs Res*. Elsevier Science (USA); 2003:9-21. vol. 1.

76. Wildes TM, Depp B, Colditz G, Stark S. Fall-risk prediction in older adults with cancer: an unmet need. *Support Care Cancer*. Sep 2016;24(9):3681-3684.

77. Chotiyarnwong P, McCloskey E, Eastell R, et al. A Pooled Analysis of Fall Incidence From Placebo-Controlled Trials of Denosumab. *J Bone Miner Res*. Jun 2020;35(6):1014-1021.

78. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. © 2017 Elsevier Ltd; 2017:513-523. vol. 7.

79. Wei FL, Gao QY, Zhu KL, et al. Efficacy and safety of pharmacologic therapies for prevention of osteoporotic vertebral fractures in postmenopausal women. *Heliyon*. Feb 2023;9(2):e11880.

80. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. *J Bone Miner Res*. Jun 2017;32(6):1291-1296. https://doi.org/10.1002/jbmr.3110.

81. Brown JP, Roux C, Törring O, et al. Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. *J Bone Miner Res*. Apr 2013;28(4):746-752.

82. Reid IR, Horne AM, Mihov B, et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. *N Engl J Med*. Dec 20 2018;379(25):2407-2416. https://doi.org/10.1056/NEJMoa1808082.

83. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer*. Aug 2008;16(8):879-889. https://doi.org/10.1007/s00520-008-0418-0.

84. Guise T. Examining the metastatic niche: targeting the microenvironment. *Semin Oncol*. © 2010. Published by Elsevier Inc.; 2010:S2-S14.

85. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*. 2001 Harcourt Publishers Ltd.;2001:165-176. vol. 3.

86. Weinfurt KP, Li Y, Castel LD, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol*. 2005:579-584. vol. 4.

87. Fizazi K, Herrmann K, Krause BJ, et al. Health-related quality of life and pain outcomes with [(177)Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. © 2023 Elsevier Ltd; 2023: 597-610. vol. 6.

88. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. *J Clin Oncol*. Nov 10 2020;38(32):3763-3772.

89. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004 Massachusetts Medical Society. 2004:1502-1512. vol. 15.

90. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004 Massachusetts Medical Society.; 2004:1513-1520. vol. 15.

91. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. Jan 10 2013;368(2):138-148.

92. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. Jul 31 2014;371(5):424-433.

93. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. May 26 2011;364(21):1995-2005.

94. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. Jul 18 2013;369(3):213-223. https://doi.org/10.1056/NEJMoa1213755.

95. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. © 2019 Elsevier Ltd; 2019:408-419. vol. 3.

96. EMA restricts use of prostate cancer medicine XOFIGO. Available at https://www.ema.europa.eu/en/news/ema-restricts-use-prostatecancer-medicine-xofigo. Accessed July 14, 2023.

97. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. © 2020. Published by Elsevier B.V.; 2021:243-262. vol. 2.

98. Rizzo S, Galvano A, Pantano F, et al. The effects of enzalutamide and abiraterone on skeletal related events and bone radiological progression free survival in castration resistant prostate cancer patients: An indirect comparison of randomized controlled trials. *Crit Rev Oncol Hematol*. © 2017 Elsevier B.V; 2017:227-233.

99. Engel-Nitz N, Behl AS, Blauer-Peterson C, Dawson NA. Real world skeletal related events (SREs) associated with oral treatments in patients with metastatic castration resistant prostate cancer (mCRPC). *Journal of Clinical Oncology*. 2023/07/14 2016;34(15_suppl):e16537-e16537. https://doi.org/10.1200/JCO.2016.34.15_suppl.e16537.

100. Saad F, Shore N, Van Poppel H, et al. Impact of bone-targeted therapies in chemotherapy-naïve metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: post hoc analysis of study COU-AA-302. *Eur Urol*. Oct 2015;68(4):570-577.

101. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. Mar 5 2011;377(9768):813-822.

102. Ueno S, Mizokami A, Fukagai T, et al. Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study. *Anticancer Res*. 2013:3837-3844. vol. 9.

103. AlZahrani M, Clemons M, Vandermeer L, et al. Real-world practice patterns and attitudes towards de-escalation of bone-modifying agents in patients with bone metastases from breast and prostate cancer: A physician survey. *J Bone Oncol*. Feb 2021;26:100339.

104. Qian Y, Bhowmik D, Kachru N, Hernandez RK. Longitudinal patterns of bone-targeted agent use among patients with solid tumors and bone metastases in the United States. *Support Care Cancer*. Jun 2017;25(6): 1845-1851.

105. George DJ, Sartor O, Miller K, et al. Treatment Patterns and Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer in a Real-world Clinical Practice Setting in the United States. *Clin Genitourin Cancer*. © 2020 The Authors. Published by Elsevier Inc; 2020: 284-294. vol. 4.

106. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer

progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. © 2010 Elsevier Ltd; 2010:1147-1154. vol. 9747.

107. Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. Dec 10 2020;383(24):2345-2357. https://doi.org/10.1056/NEJMoa2022485.

108. Jiang L, Cui X, Ma H, Tang X. Comparison of denosumab and zoledronic acid for the treatment of solid tumors and multiple myeloma with bone metastasis: a systematic review and meta-analysis based on randomized controlled trials. *J Orthop Surg Res*. Jun 22 2021;16(1):400.

109. Body JJ, von Moos R, Rider A, et al. A real-world study assessing the use of bone-targeted agents and their impact on bone metastases in patients with prostate cancer treated in clinical practice in Europe. *J Bone Oncol*. Feb 2019;14:100212.

110. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. *Lancet Oncol*. © 2013 Elsevier Ltd; 2013:663-670. vol. 7.

111. Clemons M, Liu M, Stober C, et al. Two-year results of a randomised trial comparing 4- versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. *J Bone Oncol*. Oct 2021;30:100388.

112. Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol*. 2009:1564-1571. vol. 10.

113. Ikesue H, Doi K, Morimoto M, et al. Switching from zoledronic acid to denosumab increases the risk for developing medication-related osteonecrosis of the jaw in patients with bone metastases. *Cancer Chemother Pharmacol*. Jun 2021;87(6):871-877.

114. Meulenbeld HJ, van Werkhoven ED, Coenen JL, et al. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). *Eur J Cancer*. © 2012 Elsevier Ltd; 2012:2993-3000. vol. 16.

115. Ernst DS, Tannock IF, Winquist EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol*. 2003:3335-3342. vol. 17.

116. Smith JA Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *J Urol*. 1989:85-87. vol. 1.

117. Macherey S, Monsef I, Jahn F, et al. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev*. Dec 26 2017;12(12):CD006250.

118. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. Oct 2 2002;94(19):1458-1468. https://doi.org/10.1093/jnci/94.19.1458.

119. EORTC Preliminary results confirm that the addition of bone-protecting agents to Radium-233 (Ra-233) treatment can limit fractures in metastatic castration resistant prostate cancer patients. Available at https://www.eortc.org/blog/2019/05/31/preliminary-results-confirm-that-the-addition-of-bone-protecting-agents-to-radium-233-ra-233-treatment-can-limit-fractures-in-metastatic-castration-resistant-prostate-cancer-patients-2/. Accessed July 14, 2023.

120. Ravosa MJ, Ning J, Liu Y, Stack MS. Bisphosphonate effects on the behaviour of oral epithelial cells and oral fibroblasts. *Arch Oral Biol*. © 2010 Elsevier Ltd; 2011:491-498. vol. 5.

121. Wutzl A, Pohl S, Sulzbacher I, et al. Factors influencing surgical treatment of bisphosphonate-related osteonecrosis of the jaws. *Head Neck*. Feb 2012;34(2):194-200. https://doi.org/10.1002/hed.21708.

122. Heggendorn FL, Leite TC, Cunha KS, et al. Bisphosphonate-related osteonecrosis of the jaws: Report of a case using conservative protocol. *Spec Care Dentist*. Jan 2016;36(1):43-47. https://doi.org/10.1111/scd.12143.

123. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. © 2014 American Association of Oral and Maxillofacial Surgeons. Published by Elsevier Inc; 2014:1938-1956. vol. 10.

124. Nisi M, La Ferla F, Karapetsa D, et al. Conservative surgical management of patients with bisphosphonate-related osteonecrosis of the jaws: a series of 120 patients. *Br J Oral Maxillofac Surg*. © 2016 The British Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd; 2016:930-935. vol. 8.