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Research Paper

Medication related osteonecrosis (MRONJ) in the management of CTIBL in breast and prostate cancer patients. Joint report by SIPMO AND SIOMMMS

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HIGHLIGHTS

- The BMA schedule for CTIBL are about the same than in osteoporosis.
- The risk of MRONJ in CTIBL is assumed to be similar to that in osteoporosis.
- The prevention of MRONJ in CTIBL should be differentiate from that in SRE prevention.
- Changing the treatment schedule in bone metastatic disease increases the risk of MRONJ.

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ABSTRACT

Background: Low-doses of bone modifying agents (LD-BMAs) compared to those used to treat bone metastases are used in breast or prostate cancer patients on adjuvant endocrine therapy to prevent Cancer Treatment Induced Bone Loss (CTIBL). Their use is associated with an increased risk of developing Medication-Related Osteonecrosis of the Jaw (MRONJ). However, there is not clarity about strategies aimed to minimize the MRONJ risk in cancer patients at different conditions as low- vs high-doses of BMA. This joint report from the Italian Societies of Oral Pathology and Medicine (SIPMO) and of Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS) aims to define the dental management of breast and prostate cancer patients with CTIBL under LD-BMAs, to reduce their risk to develop MRONJ.

Methods: This interdisciplinary SIPMO-SIOMMMS Expert Italian Panel reviewed the available international scientific literature and developed a set of recommendations to implement strategies of MRONJ prevention in breast (BC) and prostate cancer (PC) patients undertaking LD-BMAs to prevent CTIBL.

Results: The Expert Panel, after addressing some introductive topics (i.e., CTIBL and its management, pharmacology and pharmacodynamics of BMAs, definition and diagnosis of MRONJ), developed a joint report on the following five issues: a) prevention and dental management in cancer patients candidates to LD-BMAs, or under

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LD-BMAs; b) prophylactic drug holiday; c) MRONJ treatment; d) LD-BMAs therapeutic drug holiday; and e) restart of LD-BMA treatment after successful healing of MRONJ.
Finally, ten key questions with answers were prepared and placed at the end of the document.
Conclusions: Despite obvious weaknesses of the available international literature, the Expert Panel recognized the need to tailor separate MRONJ preventive approach for breast and prostate cancer patients on adjuvant endocrine therapy who begin low-dose BMA therapy to prevent CTIBL and provided this practical guidance for bone specialists and oral healthcare providers. In view of a MRONJ risk for BC and PC patients receiving low-dose BMAs, which approximates that of patients with osteoporosis and other non-malignant diseases undergoing similar treatment schedules, the SIPMO-SIOMMMS Expert Panel recognizes the need for less stringent preventive strategies than those already developed for BC or PC patients with bone metastases taking HD-BMAs.

1. Introduction

Breast cancer (BC) and prostate cancer (PC) are the two most common malignant disease in women and in men worldwide [1–3]. About 70–80 % of early breast cancer (BC) patients receive adjuvant endocrine therapy (AET) for at least 5 years, extended to 10 years in certain high-risk breast cancer patient populations to improve disease-free survival. [4,5]. Prostate cancer patient in which ADT in able to maintain a condition of castration with testosterone levels less than 20 ng/d are defined hormone-sensitive [6] For many years, androgen deprivation therapy (ADT) has been the standard of care for patients requiring systemic therapy; to date, the combination with new hormone therapies (NHT), have been shown to be more effective in the stage of hormonal sensitivity [7,8].

In both breast and prostate cancer survival is improving (5-year survival rate of 92 % and a 10-year survival rate of 90 %) as a result of new treatment strategies. Despite benefits associated with adjuvant hormonal therapies, these treatments cause several side-effects, including impairment of bone health, known as Cancer-Treatment Induced Bone Loss (CTIBL) [9–11]. The CTIBL is a condition characterized by bone fragility y and is managed with antiresorptive drugs (AR), such as bisphosphonates (BPs) or denosumab (DMB), generally at the doses used in postmenopausal osteoprosis [9,12].

Osteonecrosis of the Jaw (ONJ) is a potentially severe and debilitating condition that was initially reported only in patients treated with BPs [13]. With the introduction of a new antiresorptive drug (e.g., DMB) and several cancer medications with an angiogenic activity (e.g., tyrosine kinase inhibitors [TKIs], mammalian target of rapamycin [mTOR] inhibitors and anti-VEGF antibody, [bevacizumab]), which were soon associated with an increased risk of ONJ development, the definition of ONJ has been expanded to embrace all these different forms of ONJ under the term Medication-Related Osteonecrosis of the jaw (MRONJ) [14]. Among the new categories of patients that are being recognized at increased MRONJ risk, there are BC female and PC male patients receiving low doses of bone modifying agents (LD-BMAs) to manage CTIBL due to hormonal adjuvant therapy [13–16].

Up to date, four main categories of patients have been documented at increased risk of MRONJ development. In detail:

I) Cancer patients with Bone Metastases or Multiple Myeloma, commonly receiving monthly high doses of BMAs (HD-BMAs) in combination or not with other drugs (e.g., chemotherapy, anti-angiogenic drugs and other biological agents), or, rarely, receiving anti-angiogenic drugs alone (highest risk of MRONJ onset) [17,18];
II) Patients with osteoporosis and other non-malignant diseases receiving LD-BMAs (low risk of MRONJ onset) [19];
III) BC or PC patients on AET receiving LD-BMAs for CTIBL management this population is considered assumable to this with osteoporosis for what concerns their risk of MRONJ development [15];
IV) Patients with Giant Cell Tumor of Bone; commonly these patients are treated for years with a monthly injection of DMB 120 mg (HD-DMB) [20];

Regarding BC or PC hormone-sensitive patients receiving LD-BMAs for CTIBL treatment, there are limited data from clinical trials to precisely quantify the risk of patients in the latter category. In BC patients treated with LD-BMAs in the “CTIBL prevention” setting, no MRONJ adjudicated cases were reported in some trials after ZOL (4 mg every 6 months) [21,22] or DMB (60 mg every 6 months) [23], but some cases were reported after prolonged observation or careful dental follow-up evaluation [24,25]. More cases were reported in clinical trials in the “adjuvant” setting: MRONJ development ranged between 0.3 % and 5 %, after different drug schedules and, above all, with BMAs doses higher than those used for the “CTIBL prevention” setting [10,26–32].

The aim of this Joint report from the Italian Societies of Oral Pathology and Medicine (SIPMO) and the Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS) Experts Panel was to develop a set of recommendations to implement strategies of MRONJ prevention and treatment in BC and PC patients receiving LD-BMAs therapy to counteract CTIBL. The present joint report was endorsed by the following Scientific Societies: Italian Society of Osteoncology (ISO), Italian Network of Supportive Care in Oncology (NICSO), Italian Association of Medical Oncology (AIOM) and Association of medical Endocrinology (AME).

2. Hormone adjuvant therapies

Adjuvant aromatase inhibitor (AI) therapy is integral to the management of breast cancer that express estrone receptor. In postmenopausal women, aromatase induces androgen conversion to estrogen in the adrenal gland and peripheral tissues [13,14]. Aromatase inhibitors include non-steroidal aromatase inhibitors (anastrazole, letrozole) that competitively inhibit aromatase and steroidal aromatase inhibitors (exemestane) that bind irreversibly. AET options for premenopausal women ER + include tamoxifen with or without ovarian suppression (OS) with LHRH agonist (goserelin) or with ovarian ablation (OA), an aromatase inhibitor (AI) with OS/OA, or OS/OA alone. In PC hormone sensitive ADT aims to suppress testosterone levels to castration levels using GnRH agonists or GnRH antagonists [33,34]. GnRH antagonists actually should be preferred for a more rapid suppression of testosterone levels. Recently in advanced prostate cancer Androgen receptor Signaling Inhibitors (ARSI) are approved. These drugs target the androgen receptor pathway preventing androgens from stimulating cancer cell growth. Common ARSIs are abiraterone acetate, enzalutamide, apalutamide, darolutamide that are usually prescribed associated to GnRH agonist [35].

3. CTIBL and its management

The severe tissue hypoestrogenism induced by AET in women with BC and ADT in hormone-sensitive PC induces a significant acceleration of bone turnover with a rapid increase of bone loss and bone quality deterioration that increase the risk of fragility fracture [36–39].

BC on AI have 1.5–2 times higher risk of fractures compared to those on tamoxifene or no treatment. AI cause rapid bone loss at lumbar spine and hip with an annual reduction in BMD of 2–4 % The fracture risk, occurs within the first 2–5 years of AI therapy [39]. Similarly to BC, in

hormone-sensitive PC ADT cause rapid bone loss with 2–5 % annual reduction particularly during the first 1–2 years of treatment. Men on ADT have a 1.5–3 times higher risk of bone fractures compared to those not on ADT [39,40].

In clinical practice, the risk of bone fracture due to adjuvant hormone therapy is itself sufficient to justify anti-fracture therapy [39,41].

The time to start treatment to prevent CTIBL and related fractures is not accurately defined. It has been recommended to use a BMD T-score threshold lower than −1 and other fracture risk [42–45].

Therefore, in consideration of: a) the rapidity of occurrence of fractures with the onset of hormone therapy; b) the lack of a validated densitometric threshold in this setting of patients; c) the evidence that a treatment for CTIBL prevention carried out in upfront is more efficient than one started later [24,39,40,44–49], the Guidelines of the Italian National Society of Medical Oncology (AIOM) recommend, both in BC ER + and PC hormone sensitive, that inhibitors of bone resorption should be considered from the beginning of hormone therapy itself (primary prevention of CTIBL) and the Italian Medicine Agency (AIFA) reimburse the antiresorptive therapy with this indication [9,16,50]. Bisphosphonates and denosumab are effective in prevent bone loss in both BC women on AET and PC on ADT.

Oral amino bisphosphonates (BPs) such as alendronate, risedronate and ibandronate, in Italy are prescribed in postmenopausal women with BC at the same doses used in postmenopausal osteoporosis to reduce the risk of fracture. These drugs compared to controls have been shown to prevent bone loss with a modest increase in BMD at the spine and at the hip [42,43].

Zoledronic acid (ZOL) was effective to increase BMD in BC on AI when administred upfont at the dose of 4 mg/6 months that is quite higher than that approved for postmenopausal osteoporosis (5 mg/year) [24,49]. Also, for CTIBL, in male with PC oral BPs, as alendronate, risedronate were used at the same doses used in male osteoporosis and ZOL with higher dose than that used in osteoporosis (4 m/6 months vs 5 mg/year with preservation or a modest improvement of BMD, mainly at spine level. None of these studies has the end point of reducing fracture risk [24,43,49].

Only studies on DNB 60 mg/6 months have shown a significant reduction of frature risk in women with early BC treated with aromatase inhibitors and in men with BC on ADT [51,52].

The optimal duration of treatment with BPs or DMB in women with BC or males with PC is not well defined. It may be reasonably recommended that it should be continued at least for the period of treatment with hormonal adjuvant therapy. In some RCTs, the discontinuation of hormonal adjuvant therapy apparently reduces the number of fractures and that at least part of the bone mass seems to be recovered [47,53–55].

4. Pharmacology and pharmacodynamics of BMAs

The first BMAs approved for osteoporosis were BPs, synthetic analogues of pyrophosphate compounds able to fixate selectively on the bone surfaces subject to remodelling. They block osteoclast activity and reduce bone turnover, thus reducing bone fragility fractures by increasing the BMD [56].

Despite possessing identical core structures, the BPs differ widely in their affinity for bone mineral, antiresorptive potency and bioavailability [57].

These differences are due to variations in their structure and mode of administration. Oral BPs are alendronate (70 mg once weekly) and risedronate (35 mg once weekly or 75 mg for two consecutive days each month). Ibandronate is the only bisphosphonate that can be administered orally at the dosage of 150 mg once a month or intravenously at 3 mg iv every 3 months. Also, pamidronate can be administered orally or intravenously, however it not currently used for osteoporosis treatment. The only bisphosphonate that can be administered once a year for the treatment of osteoporosis is ZOL (5 mg/iv/year).

The absorbed BPs are taken up by the bones and the remaining is eliminated unchanged by the kidneys. They cannot be administered to patients with a creatinine clearance lower than 35 ml/min, while for ibandronate lower than 30 ml/min.

A unique feature of the BPs drug class is their characteristic pharmacokinetics that relates to their prolonged binding to the mineral matrix [57].

Once BPs are discontinued, they remain in the skeleton for a long time, depending on their affinity for bone, duration of administration, and degree of bone turnover. ZOL appears to have the highest skeletal binding affinity, followed by alendronate, ibandronate and risedronate. Clinically, their residual ability to suppress bone turnover, once discontinued, can be monitored, in clinical settings, through measurement of blood bone turnover markers.

The second type of BMAs approved for the treatment of osteoporosis was DNB, an IgG2 monoclonal antibody directed against RANKL (receptor activator of nuclear factor kappa-B ligand). For this purpose, at the dosage of 60 mg administered subcutaneously every 6 months, DNB suppress bone turnover, increase BMD and reduce bone fractures by inhibiting osteoclast formation, activity and survival. The clearance of DNB is like other antibodies, it is cleared via the reticuloendothelial system, with a half-life of approximately 26 days, thus DNB can be prescribed in patients with creatinine clearance lower than 35 ml/min [58].

Due to the different pharmacodynamics and pharmacokinetics compared to BPs, discontinuation of DNB is followed by an abrupt increase in bone turnover, and by a rapid loss of BMD. An increased fracture risk has been observed in patients with osteoporosis that discontinued DNB. BPs therapy may potentially diminish the loss of BMD gains attained with DNB and are suggested after DNB discontinuation [55].

It is important to note that both DNB and ZOL, among the BPs, are currently used in clinical practice for the prevention of CTIBL, using the same dosage as for osteoporosis treatment. For the treatment of skeletal-related events (SREs) in patients with bone metastases, the dosage of these drugs is significantly higher compared to that used for osteoporosis treatment [55,57].

Additionally, the timing suggested for their administration is significantly shorter compared to that used for the treatment of osteoporosis. ZOL 4 mg iv is administered every 3–4 weeks for bone metastases [59], while DMB is prescribed at the dosage of 120 mg s.c. every 4 weeks [58].

5. Definition and diagnosis of MRONJ

The expert Panel embraces the definition proposed by SIPMO-SICMF (Italian Societies of Oral Pathology and Medicine and of Maxillofacial Surgery) that defined MRONJ as “an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment” [60,61].

Patients may be affected by MRONJ if all the following criteria are satisfied [61,62]:

- Current or previous treatment with BMAs and/or antiangiogenic agents (AAs);
- Clinical and radiological findings of progressive bone destruction;
- No history of radiation therapy to the jaws or the presence of primary oral malignancy or metastatic disease to the jaws.

Despite the exposure of necrotic bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, there are several other clinical signs and symptoms associated with MRONJ (Table S1) [61,63]. The most frequently described symptoms are pain, though it is absent at MRONJ onset in many patients, and the numbness of the lips (e.g., numb chin syndrome, Vincent’s symptom) [64–67].

Also, the Expert Panel acknowledges the diagnostic work-up of MRONJ and the staging system proposed by the SIPMO-SICMF, which is based on the clinical and radiologic features of the disease (Fig. 1) [68]. Therefore, MRONJ diagnosis can be only displayed in the presence of concurrent clinical and radiologic signs of disease.

Plain radiographs (e.g., dental x-rays and panoramic radiographs) are the radiographic standard of care in routine dental practice and can support the clinician to evaluate bone changes suggestive of MRONJ, with minimal radiation exposure [69,70].

However, second-line CT-based imaging modalities, such as Cone-Beam (CBCT) and multidetector computed tomography (MDCT), are required to confirm diagnosis of suspected MRONJ cases, classify them properly and assign treatments accordingly (Table S2) [71–73].

The SIPMO-SICMF staging of MRONJ is a 3-stage clinical-radiological classification system that is centred on the presence of bone marrow sclerosis at CT-based imaging, in adjunct to the patient's clinical findings (Table S3) [61].

5.1. Methods

The SIPMO-SIOMMMS Expert Panel was established in 2023, and the Board Panel comprised a multidisciplinary group of clinicians and researchers with a special interest in MRONJ. They were asked to review the available data on BMAs and MRONJ in BC and PC patients receiving LD-BMA to prevent CTIBL.

Clinical implications for medical and dental professionals were then presented in the following Sections:

A. Dental management of the cancer patient who is a candidate for or already on LD-BMAs;
B. Temporary suspension of ONJ-related drug therapy before invasive dental procedures (Prophylactic drug holiday);
C. Treatment of MRONJ;
D. Temporary suspension of LD-BMAs with curative intent (Therapeutic drug holiday); and
E. Resumption of LD-BMAs after successful healing of MRONJ.

Finally, 10 key questions with answers were processed, and placed at the end of the document (Table 1).

We selected randomized controlled trials (RCTs), *meta*-analyzes, systematic reviews, and observational studies that investigated the prevention and management strategies of medication related osteonecrosis (MRONJ) in breast and prostate cancer patients.

In particular, the Panel included studies conducted in patients with CTIBL treated with bone antiresorptive agents, irrespective of dosing and regimen administered. We excluded studies reporting non-primary research, studies lacking a primary outcome related to the relationship between antiresorptive agents and MRONJ, review articles, and non-English language publications. Although the literature search was very detailed, this is not a systematic review as we have focused on the latest *meta*-analyzes and systematic reviews, but some minor papers may not have been included. Five different investigators (FB, GC, VF, AB and RM) independently searched papers, screened titles and abstracts of the retrieved articles, reviewed the full-texts, selected articles for their inclusion, and prepared the initial draft. FB, GC, VF, AB and RM conceptualized the topic of the review, supervised the procedure and critically reviewed the manuscript. All the other authors critically reviewed the manuscript.

A Prevention and Dental Management of BC and PC cancer patients who are candidates to LD-BMA therapy.

The most effective strategy to prevent MRONJ is the adoption of oral health preventive measures prior to, during and even after the initiation of treatment with ONJ-related drugs [60,74,75].

Since the recent implementation in daily practice across the world of

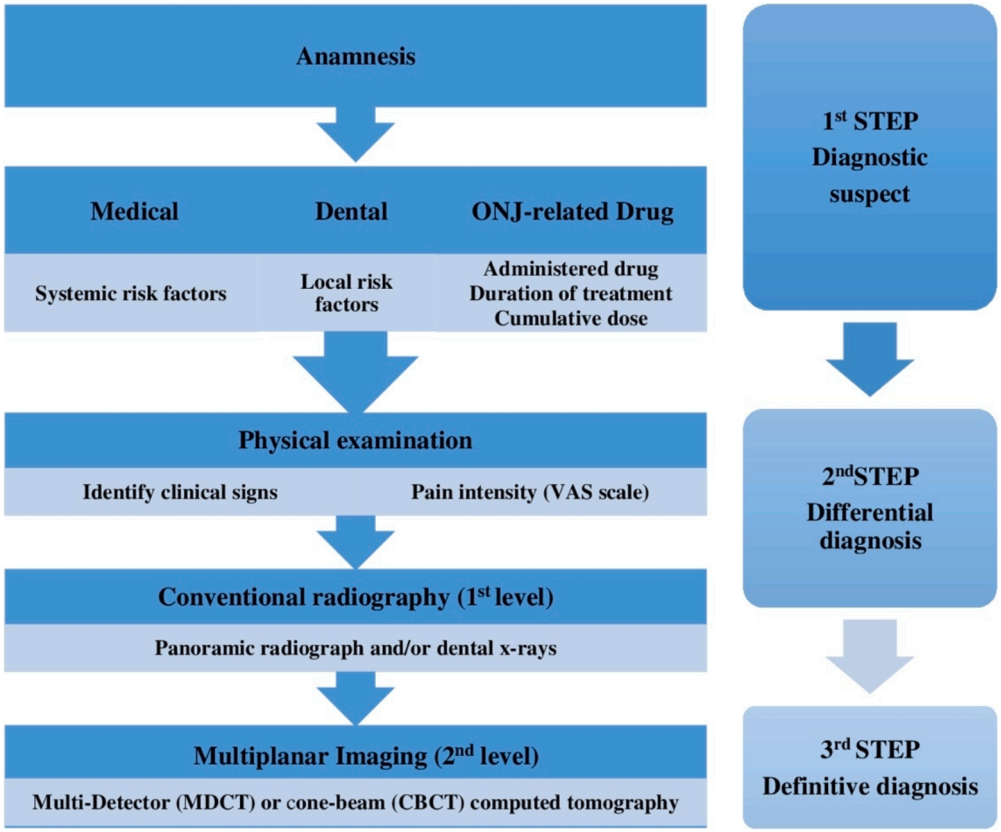


Fig. 1. Diagnostic Work-up of MRONJ (from Bedogni et al, 2024) [60].

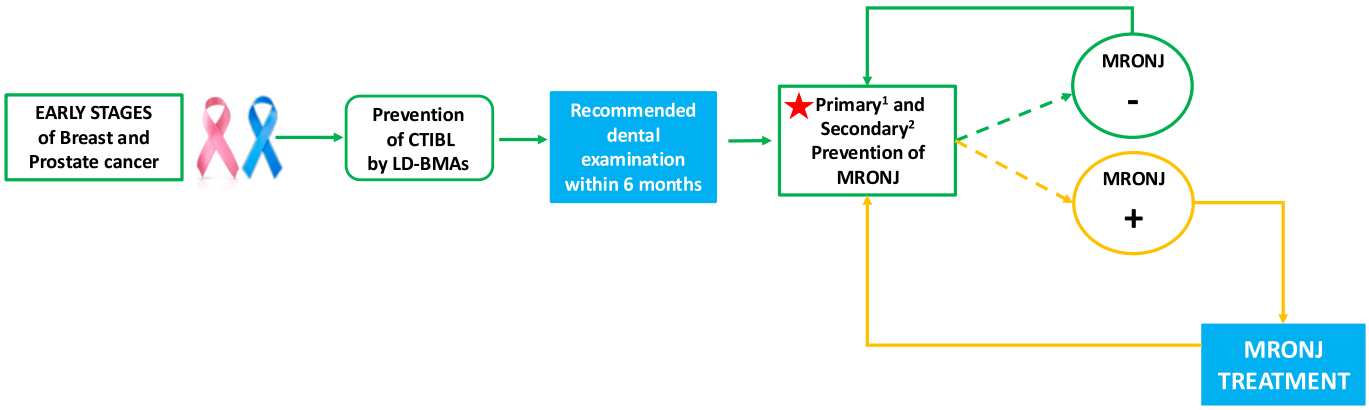
Table 1
SIPMO-SIOMMMS 10 Key questions.

Key questions	
Q1	**Is the risk (incidence) of MRONJ in patients treated with antiresorptive drugs (BPs, DMB 60 mg) comparable to that of patients treated with these drugs at doses used to prevent complications from bone metastases in solid tumors and multiple myeloma** No, the risk is not comparable. Patients receiving antiresorptive drugs for CTIBL have a MRONJ risk similar to that of patients with osteoporosis treated with the same drugs and dosages, which is significantly lower (<1%) than the risk of cancer patients with bone metastases and Myeloma patients receiving HD-BMAs. The risk for these patients ranges from 1 % to 20 % or more, depending on the duration of treatment and the observation period.
Q2	**In patients scheduled for treatment with antiresorptive drugs (BPs, DNB) for the prevention of CTIBL, which procedures should be implemented to mitigate the risk of MRONJ?** In patients scheduled for treatment with antiresorptive drugs (BPs or DNB) for CTIBL prevention, an assessment of oral health status – including dental, periodontal, *peri*-implant examination (where dental implants are present) and panoramic radiography – should be conducted before starting the therapy or, at the latest, within the first six months of treatment. Any necessary dental procedure should be coordinated between the dentist and the bone specialist or prescribing physician to ensure timely intervention, preferably before the therapy begins.
Q3	**In patients treated with antiresorptive drugs (BPs, DNB) for the prevention of CTIBL, should dental follow-up be scheduled differently from that for patients with osteoporosis?** In patients treated with antiresorptive drugs (BPs and DNB) for the prevention of CTIBL, regular dental follow-up should be scheduled by the dentist every 6 months, similar to the approach for patients with osteoporosis, and less frequently than for oncology patients treated for bone metastases (who typically have follow-ups every 4 months). Special attention should be given to active dental/periodontal/*peri*-implant diseases, which need to be actively addressed and monitored (even on a monthly basis).
Q4	**In patients treated with BPs for the prevention of CTIBL, should these medications be temporarily interrupted before an invasive dental procedure?** In patients treated with oral or i.v. BPs for less than 3 years, the discontinuation is not indicated. In patients treated with oral BPs for more than 3 years, these could be discontinued 1 week before the procedure and resumed when the oral mucosa is completely healed (4–6 weeks after the dental procedure)[68]. In patients treated with i.v. 5 mg ZOL, due to its high skeletal binding affinity, any elective dental surgical procedure should ideally be scheduled about 12 months after the last ZOL infusion. (by one or few months). The subsequent infusion can be delayed until the oral mucosa is completely healed. (typically, 4–6 weeks after surgery). In case dental surgical procedures are emergent, and the patient recently had the annual zoledronic acid (ZOL) infusion, a common approach is to wait at least 1 week after the last infusion before performing the procedure [60].
Q5	**In patients treated with DNB for the prevention of CTIBL, should this medication be temporarily interrupted before an invasive dental procedure?** Discontinuation of DNB is followed by a sudden increase of bone turnover, rapid loss of BMD and an increase in vertebral fractures, knows as the rebound phenomenon. Therefore, prophylactic discontinuation of DNB is always contraindicated. In patients who have been treated for more than 3 years with DNB, BPs, or a combination of both or who present other systemic (e.g., concomitant use of corticosteroids, diabetes, and rheumatoid arthritis), a "safety window" may be identified. This safety window typically lasts about 2 months, beginning ideally 5 months after the last dose of DMB and ending no later than the start of the 7th month. Delaying the next dose by 1 month is advisable when the oral mucosa is completely healed. It is crucial to communicate with the bone specialist about the feasibility of this potential delay.
Q6	**In patients treated with antiresorptive durgs (BPs or DNB) for the prevention of CTIBL, if these medications are suspended before an invasive dental procedure, when should they be resumed?** In the case of a prophylactic bisphosphonate (BPs) holiday, therapy should be resumed once the oral mucosa is completely healed, typically about 4–6 weeks after the dental procedure. There is no evidence that extending the drug holiday beyond this period is effective. In DNB treated patients the dose could be delayed after invasive dental procedure maximum for 30–45 days.
Q7	**In patients treated with antiresorptive drugs (BPs, DMB) for the prevention of CTIBL, if they develop bone metastases and subsequently transition to high-dose antiresorptive therapy for the prevention of SREs, would the strategies for preventing MRONJ change?** In patients switching from low-dose to high-dose antiresorptive drugs (BPs, DNB), oral health status should be assessed through dental examination and panoramic radiography before starting high-dose BMAs and all emergent oral and dental triggers addressed. Additionally, dental follow-up visits should be scheduled every 4 months or monthly if active dental, periodontal, or *peri*-implant diseases are present.
Q8	**In patients treated with antiresorptive drugs (BPs, DNB) for the prevention of CTIBL, in the event of suspected or confirmed diagnosis of MRONJ, is the reporting adverse drug reactions to Pharmacovigilance Authorities recommended? Who is obligated to make this report?** Based on national regulations, all oral healthcare providers (including prescribing physicians, dentists, and maxillofacial surgeons) should report every case of adverse drug events, including MRONJ, to their Pharmacovigilance Authorities.
Q9	**In patients undergoing antiresorptive therapy (with BPs,DNB) for CTIBL prevention, if MRONJ develops, is it advisable to consider an alternative therapy for fracture risk prevention during the MRONJ treatment period?** Teriparatide may be considered as an alternative in CTIBL therapy to bisphosphonates or denosumab if these are to be suspended for the appearance of MRON for the time needed for healing. Some data also suggest a potential benefit on the healing of MRONJ. The decision to use TPTD should be carefully considered, involving a thorough individual risk assessment by the treating physician in collaboration with the patient, weighing the proven benefits against potential safety concerns is a recombinant fragment of human parathyroid hormone consisting of the first 34 amino acids of the N-terminal region, which exerts effective osteoanabolic action. In patients treated with amino-bisphosphonates for bone metastases or multiple myeloma, daily subcutaneous TPTD has been shown to promote bone healing and improve the resolution rate of MRONJ. However, TPTD is contraindicated in individuals with active bone malignant tumors, those with bone metastases and those who have undergone skeletal radiation. In Italy, the use of teriparatide for this clinical indication is off label. To date, no other bone-active therapies are recommended in this clinical context.
Q10	**Following the healing of MRONJ, is it possible or advisable to resume antiresorptive therapy (BPs, DMB) to prevent skeletal fragility?** The resumption of therapy for CTIBL after MRONJ healing is not extensively covered in the literature but remains of significant interest in clinical practice. Preventing fractures, especially in high-risk conditions like CTIBL, continues to be important even after MRONJ has resolved. There is no rationale for not resuming anti-fracture therapy after the healing of MRONJ, Resumption of BP or DNB therapy following healing of MRONJ lesions has been suggested although the evidence is weak, and apparently subsequent local recurrence had not been reported. Given the heterogeneity of patients involved, the degree of fracture risk, previous CTIBL therapy, ongoing hormone adjuvant therapy and its residual duration, it is advisable to refer the patient to a Centre for Osteoporosis & Bone Health, who collaborates closely with an oral or Maxillofacial Surgery Centre.

LD-BMA therapy to prevent CTIBL in non-metastatic BC and PC patients, there is no consensus yet on the preventive measures and dental management strategies to be adopted in this patient population. However, since BC and PC patients taking low-dose BMAs have a risk of MRONJ comparable to that of patients with osteoporosis (OP) and other non-malignant diseases taking LD-BMAs, the Expert Panel believes that the same preventive measures already in use for OP patients should be applied in this setting.

In general, the aim of primary prevention in patients at risk of MRONJ development is to identify and treat all oral conditions able to trigger MRONJ and to maintain a sound oral health over time. A pre-treatment oral assessment is not mandatory for patients about to start LD-BMA therapy, because they display low to null risk of MRONJ as compared with the general population in the first few years of treatment. Worthy of note, according to SIPMO-SICMF recommendations, it is advisable for patients starting low-dose BMAs to undergo an oral assessment—evaluating dental, periodontal, and *peri*-implant status, as well as the quality of restorations and prostheses—within six months from the start of therapy (Fig. 2) [60,61].

MRONJ prevention strategies are usually classified in non-invasive dental procedures (e.g., periodontal therapy) and invasive surgical procedures (e.g., dental extraction), to be performed before or during



★ Be careful because patients may have already received AR therapy for primary or secondary osteoporosis and then may not be AR-naïve.
Acronyms- AR: Antiresorptive drugs (e.g., bisphosphonates, denosumab); CTIBL: Cancer Treatment Induced Bone Loss; SRE: Skeletal-Related Events (e.g., bone fractures, spinal cord compression)
1. Primary prevention for MRONJ consists of the elimination of local risk factors and restoring and/or maintaining good oral health before or during AR.
2. Secondary prevention for MRONJ consists of early diagnosis through follow-up examinations every 6 months (for early-stage prostate or breast cancer patients) and every 4 months (for advanced stage with bone metastases patients).

Fig. 2. Flowchart of MRONJ primary prevention pathway during treatment with LD-BMAs for CTIBL prevention.

LD-BMA therapies (see later).

A Prevention and dental management of BC and PC cancer patients taking LD-BMAs

For patients undergoing active treatment with medications associated with ONJ, periodic primary preventive oral measures should be carried out by oral healthcare providers (e.g., dentists, oral medicine practitioners, dental hygienists, oral and maxillofacial surgeons).

Treating physicians should also contribute to the patient's adherence to scheduled recall visits to reduce the risk of MRONJ onset and encourage compliance with BMAs. It is recommended to schedule recall visits every 6 months for the entire duration of BMA therapy; follow-up visit should be also planned periodically after the end of the treatment in patients receiving BPs [68,76].

Dental management include the following dental treatments:

- essential or emergent procedures aimed at removing infectious triggers (e.g., pulpitis, pericoronitis, osteitis, dental or periodontal abscess, *peri*-implantitis, dental trauma, extensive caries or defective restorations that cause pain or tissue damage, adjustments in dentures that cause damage to oral structures);
- non-essential or elective procedures, which include but are not limited to cosmetic procedures, orthodontic therapy, replacement of amalgam restorations for aesthetic reasons, elective periodontal care, intentional root canal treatment, prosthodontics and elective oral surgery.

Dental treatments, as proposed by SIPMO-SICMF, may be also classified into the following two categories based on a risk/benefit ratio for patients (Table 2) [60,61]:

- indicated treatments (green light): all essential procedures required to treat emergent oral conditions, as well as elective non-surgical

Table 2
Dental management of patients who receive LD-BMAs and are at increased of MRONJ development (modified from Bedogni et al, 2024) [60].

	Dental treatments	LD-BMAs R_x patients
Non-surgical Procedures	*Restorative dentistry*	Indicated
	Endodontic treatment	Indicated
	Orthodontic treatment	Feasible
	Periodontal therapy	Indicated
	Prosthetic rehabilitation	Feasible
Surgical Procedures*	*Dentoalveolar surgery*	Indicated
	Tooth extraction	Indicated
	Pre-implant bone surgery	Feasible
	Dental implant surgery	Feasible**
	Periodontal surgery	Indicated
	Endodontic surgery	Indicated

Legend: green shade: indicated procedures; yellow shade: feasible procedures.
* Tight soft-tissue closure must be ensured. Except for LD-DMB Rx patients who do not necessitate drug suspension before surgery, BMAs should be resumed once wound healing has been achieved (4–6 weeks).
** It is advisable to inform the patient about the long-term risk of implant-triggered MRONJ.

procedures that are indicated but have not been associated with an increased risk of MRONJ development;
- feasible treatments (yellow light): elective procedures with an uncertain risk of MRONJ under specific conditions.
- In general, all non-surgical procedures essential for resolving infectious processes are clearly indicated for all patients receiving BMAs, regardless of their individual risk of MRONJ, and should be delivered as soon as possible (e.g., restorative dentistry) [66,68]. When invasive treatments are needed (e.g., dental extraction of teeth with poor prognosis), BMA treatment should be postponed until soft-tissue healing is achieved (i.e., 4 to 6 weeks after surgical procedures) [60,76]. Overall, BMA therapy should be delayed until dental and periodontal health is optimized, if systemic conditions permit.

5.2. Dental extraction

Teeth with poor prognosis or that have failed to resolve with restorative treatment should not be declined dental extraction. Since chronic infection is the main local risk factor for MRONJ, tooth extraction has a clear preventative role of MRONJ, when properly and timely executed [66,77–80].

Patients under LD-BMAs for a period less than 3 years (in absence of other systemic risk factors) may be safely subjected to routine dental extraction. On the contrary, BC and PC patients who have been on low-dose BMAs for more than 3 years, or those with additional systemic risk factors, should undergo surgical dental extractions following specific MRONJ risk reduction protocols. These protocols typically include mucoperiosteal flap elevation, atraumatic tooth extraction, alveolectomy and smoothing of bone edges, and tension-free soft tissue closure [60,68,81–83]. In the case of surgical dental extractions in this category of patients, perioperative administration of systemic antibiotics may be prescribed as a precaution to lower the risk of MRONJ development [84].

5.3. Dental implant surgery

Dental implant placement is feasible in BC and PC patients already receiving LD-BMA therapy to prevent CTIBL, regardless of the duration of treatment (less or more than 3 years) or the type and route of administration of the medication. However, these patients should be clearly informed of the low, though non-quantifiable, risk of MRONJ onset [85–87].

Implant-related MRONJ has been categorized into early (implant surgery-triggered) or late (implant presence-triggered), with the latter being more frequent. Late implant-related MRONJ often arises in patients who underwent dental implant surgery well before the initiation of BMAs [85,86,88].

Finally, in patients treated with low-dose BMAs for more than 3 years, or in those exposed to BMAs for less than 3 years but with other systemic conditions, the immediate loading of dental implants should be considered carefully.

It is important that BC and PC patients receiving LD-BMAs are made aware of the potential risk of late MRONJ onset, as transitioning to a metastatic disease pattern that requires a shift to high-dose BMAs is not infrequent. They should also be informed about alternative strategies for the restoration of missing teeth.

B) Prophylactic drug holiday

The term “prophylactic drug holiday” refers to the discontinuation or delayed administration of BMA therapies, such as BPs and DNB, in patients at risk of MRONJ, onset before the necessary dental procedures take place. The idea of a prophylactic drug holiday arises from the observation that the uptake of bisphosphonates (BPs) is increased at bone sites involved by bone injury, where bone turnover is higher. Therefore, theoretically, a period of off-treatment may reduce BP deposition in the jawbone; it remains controversial due to limited evidence supporting strong recommendations for all patients at risk of MRONJ [11].

Talking about the “prophylactic drug holiday”, it is important to consider two aspects. First, BPs and DNB display different pharmacokinetics. Upon discontinuation, BPs persist in the skeleton for an extended period, leading to variable and prolonged inhibition of bone turnover [57]. Second, DNB interruption results in a sudden surge in bone turnover, rapid BMD loss, and an increased incidence of clinical vertebral fractures [55].

Therefore, it is of utmost importance to plan a balanced and combined assessment by both the bone specialist (to evaluate high versus low risk of fracture) and the dentist (to assess high versus low risk of post-extraction complications). This assessment helps determine whether a patient undergoing oral surgical procedures needs a precautionary interruption of bisphosphonates (BPs) or postponement of DNB), keeping in mind that discontinuation of DNB is strongly contraindicated [89].

BC and PC cancers patients treated with BMAs to prevent CTIBL receive antiresorptive drugs at the same dosage as osteoporosis patients (e.g., oral BPs; 5 mg ZOL every 12 months; 60 mg DMB every 6 months). Therefore, in the absence of additional risk factors for MRONJ and if treated with antiresorptive drugs for less than 3 years, patients should be considered at low risk for MRONJ, like patients with osteoporosis. In such cases, a prophylactic drug holiday should not be considered. [68,90,91].

When a patient is treated with DMB, after a previous BPs administration, he/she must be classified with the MRONJ risk profile considering the cumulative period of antiresorptive therapy.

A prophylactic drug holiday should be considered only in patients exposed to antiresorptive therapy for more than 3 years or in patients exposed to antiresorptive therapy for less than 3 years but in the presence of other systemic risk factors (e.g., concomitant use of corticosteroids, diabetes, or rheumatoid arthritis). The Panel acknowledge that the decision to start a drug holiday should be made jointly by the bone specialist, the oral health provider, and the patient.

In particular, for patients treated with oral BPs for more than 3 years or those exposed to BPs for less than 3 years but with other systemic diseases, BPs could be discontinued 1 week before the dental surgical procedure and resumed once the oral mucosa is completely healed (typically 4–6 weeks surgery) [68]; in the case of dental implant placement, the osseointegration process should be monitored and documented.

In patients treated with i.v.5 mg ZOL, considering its high skeletal binding affinity, any elective dental surgical procedure should ideally be scheduled about 12 months after the last ZOL infusion. The subsequent infusion can be postponed until the oral mucosa is completely healed (typically, 4–6 weeks after surgery); in case dental surgical procedures are emergent, and the patient recently had the annual zoledronic acid (ZOL) infusion, a common approach is to wait at least 1 week after the last infusion before performing the procedure. In any case, it is recommended to wait at least 4–6 weeks after the dental procedure, once the oral mucosa is completely healed, before administering the next infusion [16].

In patients treated with DNB, it is possible to take advantage of the pharmacodynamics of this drug. Indeed, after injection, DNB reaches its peak serum concentration within 4 weeks and declines over 4–5 months to a level below assay limits [89].

In the case of elective surgical procedures (e.g., preprosthetic surgery, dental extractions, and dental implant surgery), patients should ideally undergo the procedure 5 months after the last dose of DMB and delay the next injection of DNB by 1 month once soft-tissue healing has been completed (typically, 4–6 weeks after surgery). In the case of dental implant placement, the osseointegration process should be monitored and documented [90].

A 1-month delay of DNB must be authorized by the bone specialist. Indeed, patients cannot always accurately report the date of the last DNB injection, and while a delay of up to 30 days does not expose the patient

to an increased risk of fracture, a delay of even a few days longer significantly increased fractures risk, especially in patients who have been taking DNB for longer and who typically develop a greater rebound [92,93]. Communication between the bone specialist (i.e., drug prescriber) and oral and maxillofacial surgeons is essential to protect patients from the risk of severe rebound-associated vertebral fractures (RAVFs) and ensure the achievement of optimal treatment outcomes [55,94].

C) MRONJ treatment

MRONJ can be successfully managed if addressed promptly and appropriately [66,95–97]. It is documented that surgical therapy in combination with medical therapies yields more predictable results compared to nonsurgical therapy alone at all stages of disease and in the long term [98–101].

MRONJ patients can experience significant benefits from surgery in terms of improved quality of life and restoration of oral function; moreover, they can safely resume BMA therapy, when indicated [67,102,103]. In contrast to cancer patients with bone metastases or Multiple Myeloma patients who normally receive high-dose BMAs on a monthly schedule, the prognosis of MRONJ and the natural course of the disease in patients undergoing low-dose BMA treatment for CTIBL are more favourable [104]. In addition, while BPs become stably incorporated into bone tissue for long, DMB does not accumulate in the mineral matrix, and its inhibitory effect on bone turnover is transient [105].

For all these reasons, it is likely that the response to treatment, in particular to surgery, is not uniform and depends on a series of factors, which includes the patient characteristics, the underlying disease (cancer vs osteoporosis), and the type and dosage of the BMA administered.

Based on these premises and supported by initial clinical experiences [95], the Panel of SIPMO-SICMF Experts proposed in the 2020 Italian Recommendation on MRONJ the implementation of a combined medical-surgical treatment protocol. In this protocol, the intensity of surgery required to successfully treat MRONJ was not only graded on the stage and radiological extent of the disease, but also on the type of antiresorptive agent used and the specific MRONJ risk category to which the patient belongs [61]. In other words, MRONJ patients taking LD-BMAs, including BC and PC patients treated for CTIBL prevention, can benefit from much less invasive surgical interventions for all disease stages, as compared with MRONJ patients taking HD-BMAs [61].

In addition, patients receiving LD-DMB therapy who develop MRONJ, due to the peculiar pharmacodynamics of DNB, can likely be treated with even less aggressive surgery (e.g., bone curettage and/or sequestrectomy), taking advantage of the reactivation of bone turnover that commences five months after the last injection. This fact would facilitate postoperative healing [89].

A planned delay of one month from the subsequent DMB dose (60 mg every six months) could be enough to allow surgical procedures of reduced intensity compared to those required for patients taking low-dose BPs, without increasing the risk of vertebral fractures associated with DMB discontinuation [60,89]. For further details, refer to the next section “BMAs therapeutical drug holiday“.

In conclusion, surgery represents the most effective treatment of MRONJ, in combination with medical therapies. The choice between surgical and non-surgical treatment remains individualized and should always undergo careful and collaborative evaluation by the bone specialist and the surgeon.

The intensity of surgery varies depending on the disease stage at diagnosis, so an early diagnosis (i.e., initial stage) allows for healing with minimal surgical invasiveness. The necessary intensity of surgery is further reduced in patients taking low-dose BMAs, regardless of the disease stage at diagnosis, and potentially even more so in those receiving LD-DMB.

D) BMAS therapeutical drug holiday

The term “*therapeutical drug holiday*” refers to the temporary discontinuation of BMA therapies aimed to slow down or possibly halt MRONJ progression. Unfortunately, the management of antiresorptive treatment in patients who developed MRONJ is based on a very limited and weak evidence. In the absence of convincing data for the CTIBL patient’s setting, the decision to temporary interrupt BMA treatment should be closely shared between the prescribing physician, oral health provider and patient.

It is still matter of debate if BPs discontinuation can lead to an improvement of MRONJ. According to retrospective evaluations, BPs discontinuation may contribute to reduce healing time of MRONJ; therefore, few clinical guidelines support this strategy (mainly for cancer patients assuming HD-BMAs) [106–108]. However, most of clinical recommendations do not support long-term BPs withdrawal as a treatment of MRONJ, while suggest short-term BPs discontinuation when surgical therapy is indicated [60,67,109]. Due to the long-lasting inhibitory activity of BPs on bone remodelling (mainly alendronate or ZOL), it has been recently suggested to shift to teriparatide (TPD) in place of BPs when MRONJ occurs, as this may promote bone healing of MRONJ while restoring bone turnover [110]. A recent study by Sim et al. demonstrated the positive effects of TPTD on bone healing in MRONJ patients with localized or metastatic cancer disease, showing improved outcomes at one-year follow-up without the emergence of new malignancies or worsening of preexisting tumor lesions [111]. A recent metanalysis analysed a total of 111 osteoporosis patients who received TPD to treat MRONJ. TPD was used alone in 45.1 % of cases, with total MRONJ resolution being observed in 59.5 % of the individuals. In addition, MRONJ patients who had undergone treatment with TPD in combination with another therapeutic modality were 1.21 times more likely to present total resolution of osteonecrosis than those who had undergone treatment with TPD alone (CI = 1.40–1.39; $p < 0.010$)[110]. While the use of teriparatide (TPTD) for osteoporosis patients with MRONJ is a viable option given the drug’s safety profile in this context, significant safety concerns arise only regarding its use in patients with a history of skeletal irradiation or bone malignancies. Concern regarding malignancies in teriparatide users were progressively downgraded [112]. Nevertheless, the decision to use TPTD should be carefully considered, involving a thorough individual risk assessment by the treating physician in collaboration with the patient, weighing the proven benefits against potential safety concerns [113].

On the opposite, discontinuation of DMB not followed by BPs therapy causes a “rebound effect phenomenon” with consequent increased risk of multiple vertebral fractures. This finding makes DMB withdrawal generally not recommended as an adjunctive non-surgical treatment of MRONJ in non-metastatic patients treated with low-dose DMB (60 mg every 6 months) [16,60].

In this peculiar clinical setting, a planned 1-month delay of the scheduled dose of DMB might be advisable to allow surgery of reduced intensity to be done 5 months after the last DMB injection, taking advantage of the reactivated bone turnover and maintaining low the risk of “rebound vertebral fractures” [89].

Another clinical approach has been provided by Anastasilakis et al., who suggest carrying on the bone antiresorptive therapies in the earlier stages of MRONJ and to consider discontinuation in more severe ones [11].

6. Resumption of LD-BMAs after MRONJ successful healing

Resumption of BMA therapy to lower the fracture risk in BC and PC patients following successful treatment of MRONJ has not been extensively addressed in the scientific literature, although this is of great interest in the clinical daily practice. Indeed, the need to prevent fragility fractures, especially in high-risk patients receiving adjuvant hormone therapy persists once MRONJ is resolved.

There is no apparent contraindication to resume anti-fracture therapy, and preventive practices for MRONJ should probably be even more stringent and careful.

In the FREEDOM study on osteoporosis patients treated with DMB 60 mg every 6 months to reduce the risk of fracture, 13 cases of MRONJ

occurred among 3591 enrolled patients (incidence 0.36 %).

Of the 13 patients with MRONJ, 8 uninterrupted DNB after the onset of MRONJ, while 2 interrupted it because they had reached the conclusion of the study, and 3 patients who could receive DMB did not continue it after the diagnosis of MRONJ, without a specified reason [19].

Resumption of therapy with DNB or BPs after successful healing of MRONJ has been suggested by international expert consensus, although the evidence remains weak [114].

Considering the clinical heterogeneity of the patients involved, the individual fracture risk level at the time of assessment, the ongoing CTIBL therapy before the MRONJ event, the ongoing adjuvant hormonal therapy and its remaining duration, the Panel suggests to refer patients to second-level centres specialized in osteoporosis and bone health, which have close collaboration with Oral medicine and Maxillofacial surgery centres, for a final decision on the resumption of anti-fracture therapies.

7. Conclusions

Based on the available literature and the consensus of the experts involved, it was possible to establish specific strategies for the prevention of MRONJ in BC and PC patients undergoing LD-BMA therapy to prevent CTIBL. These preventive measures align with the latest Italian recommendations from SIPMO-SICMF, which focus on and implement guidelines also for BC or PC patients undergoing LD-BMAs.

Overall, the SIPMO-SIOMMMS Expert Panel acknowledges the need to personalize MRONJ preventive approaches, being less stringent with BC or PC patients who receive LD-BMAs to prevent CTIBL, while adopting specific MRONJ risk reduction strategies when these patients eventually develop bone metastases and are switched to HD-BMAs.

CRediT authorship contribution statement

Francesco Bertoldo: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization. **Cristina Eller-Vainicher :** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Vittorio Fusco:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Rodolfo Mauceri:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Jessica Pepe:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Alberto Bedogni:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Andrea Palermo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Umberto Romeo:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Giuseppe Guglielmi:** Writing – review & editing, Writing – original draft, Visualization. **Giuseppina Campisi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare no competing interests. Within the last 12 months, G.C. received honoraria for lecturing by Amgen; and F.B. has been consultant or speaker for Abiogen, Amgen, UCB pharma, Chiesi, and SPA.

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Appendix A. Supplementary data

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