Editorial

TJ Tumori Journal

Tumori Journal
2025, Vol. 111(5) 366–378

DOI: 10.1177/03008916251367339
journals.sagepub.com/home/tmj
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The use of bone-modifying agents in early breast cancer: AIOM Guidelines update and perspectives

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Abstract

Breast cancer (BC) is the leading cause of cancer-related mortality among women, with early BC (EBC) comprising most cases. Advancements in neo(adjuvant) therapies have significantly improved outcomes, although they are often associated with cancer treatment-induced bone loss, which increases the risk of fractures and negatively impacts quality of life. Bone-modifying agents (BMAs), such as bisphosphonates and denosumab can mitigate this adverse effect. By reviewing and summarizing the most recent evidence published on BMAs use in EBC, an expert Italian Panel, composed of the authors of the Italian Association of Medical Oncology (AIOM) guidelines, offers an extended clinical interpretation and updated overview of key questions and recommendation, including the optimal timing of BMAs initiation, appropriate treatment duration, and the most effective agents for fracture risk reduction. Additionally, a critical and previously unaddressed topic is also discussed: BMAs impact on survival outcomes in EBC scenario. This paper offers practical insights into bone health management for EBC patients, explores the potential survival benefits offered by BMAs, and highlights differences among international guidelines regarding their recommended use.

Keywords

Early breast cancer (EBC), Bone-modifying agents (BMAs), Cancer treatment-induced bone loss (CTIBL), Long-term outcomes, bisphosphonates (BPs), denosumab

Date received: 27 April 2025; revised: 14 July 2025; accepted: 29 July 2025

Introduction

In 2020, global estimates reported 2.3 million new cases of breast cancer (BC), including 55,000 in Italy, accounting for nearly 12% of all new cancer diagnoses.[1] With 685,000 associated deaths, BC remains the leading cause of cancer-related mortality among women worldwide.[2] Most cases, classified as early BC (EBC), can be cured with multimodal treatment, although not without side effects. Among the most common complications, cancer treatment-induced bone loss (CTIBL) and the subsequent increased risk of fragility fractures is clinically relevant, and significantly impact morbidity and quality of life.[3,4] Notably, the deterioration of bone quantity and quality occurs through various (neo)adjuvant therapies, primarily endocrine treatment (ET), but also through radiotherapy and chemotherapy, with the latter potentially inducing iatrogenic premature menopause. Moreover, concomitant medications, such as high-dose glucocorticoids, also contribute to CTIBL. Specifically ET, including tamoxifen (TAM), Gonadotropin-Releasing Hormone (GnRH) analogues, and aromatase inhibitors (AIs), represent the cornerstone of adjuvant treatment for hormone receptor-positive (HR+) EBC. Notably, they create an estrogen-deprived environment, eliminating the protective, anti-resorptive effect of estrogen on bone tissue. This accelerates the decline in bone mineral density (BMD) and increases the risk of fractures.[5] However, in the EBC setting, bone-modifying agents (BMAs) have the potential to reduce skeletal complications, including BMD loss and fractures. However, their impact on lowering the risk of (bone) recurrence and improving overall survival (OS) remains to be fully established. In December 2020 the European Society for Medical Oncology (ESMO) published the Clinical Practice Guidelines on bone health in cancer[6] with dedicated attention on BMAs use in EBC patients. In January 2022, Cancer Care Ontario (CCO) and American Society of Clinical Oncology (ASCO) released an updated joint guideline on BMAs use in the same setting, with a specific focus on their role for BC recurrence risk reduction.[7] Meanwhile, the Italian Association of Medical Oncology (Associazione Italiana di Oncologia Medica, AIOM) issued new guidelines on EBC in November 2023, and on bone metastasis and bone health in May 2024.[8,9]

The 2020 ESMO guidelines emphasized that BMAs should primarily be considered for menopausal patients who are at intermediate to high risk of recurrence, in order to reduce the risk of metastatic spread.[6] Specifically, zoledronic acid (ZOL), initiated alongside adjuvant chemotherapy and then administered every six months, or daily oral ibandronate or clodronate, can be considered for this purpose, although the optimal treatment duration remains uncertain. Conversely, although denosumab (60 mg every

six months) is not recommended for reducing recurrence, it should be the preferred option for preventing fractures in postmenopausal women with low-risk disease.

The 2022 CCO-ASCO guidelines recommend that adjuvant bisphosphonate (BPs) therapy, should be discussed with all post-menopausal EBC patients (natural or therapy-induced), irrespective of HR and human epidermal growth factor receptor 2 status (HER2), who are candidates to receive adjuvant systemic therapy, as a strategy to reduce the risk of recurrence.[7] Specifically, for this purpose, it is recommended that BPs administration begins early, alongside the initiation of (neo)adjuvant treatment, within three months of definitive surgery or two months of completing adjuvant chemotherapy. The "high-dose" regimens typically include ZOL administered intravenously (IV) at (4 mg once every six months for three years or 4 mg once every three months for two years) or daily oral clodronate (1600 mg daily for two-three years) or oral ibandronate (50 mg daily for three years). The NHS PREDICT tool can help estimate BPs benefit, which indeed depends on the underlying risk of recurrence, and may aid in shared decision-making, also considering factors such as the risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy. Conversely, denosumab is not recommended for reducing the risk of BC recurrence, as studies show inconsistent benefits.

Both the 2023 AIOM guideline on EBC[8] and the 2024 AIOM guideline on bone metastasis and bone health[9] have addressed the use of BMAs, emphasizing their role in maintaining bone health and providing skeletal protection. They recommended initiating treatment with BMAs, at the same "low-dose" recommended for women with osteoporosis, in patients with HR+ EBC who are post-menopausal, whether due to natural causes, surgery, chemotherapy, or GnRH analogues. This treatment should begin at the onset of ET, regardless of T-score values, and be continued for its entire duration. According to Agenzia Italiana del Farmaco (AIFA) Note 79 (Determination No. 589, Official Gazette No. 115 of 05/20/2015), the use of three BPs, ZOL (5 mg IV every 12 months), alendronate (70 mg orally per week ± vitamin D), and risedronate (35 mg orally per week), as well as denosumab (60 mg subcutaneously every six months), are authorized and reimbursed by the National Health Service (SSN) for the primary prevention of bone fractures (but not for survival outcomes improvement) in menopausal women undergoing adjuvant ET.

Methods

The AIOM Clinical Guidelines were developed following the AIOM standard operating procedures for guidelines development.[10] Since the publication of their most recent versions, no novel results from phase III randomized controlled trial have been published on the use of BMAs in the EBC setting. However, several notable meta-analyses, small randomized controlled studies, trial updates, and exploratory subanalyses have emerged since then, offering new perspectives.[11-18] An expert Italian panel, including the extensor of the AIOM guidelines on EBC and bone metastasis and bone health, reviewed these findings to offer an extended clinical interpretation and an updated overview of previously addressed key questions and recommendations, along with a fourth previously unexplored topic, as follows:

- **Key Question 1:** In women with breast cancer undergoing adjuvant hormone therapy, which drugs should be used to reduce the risk of fractures in CTIBL?
- **Key Question 2:** When should patients with breast cancer who are starting adjuvant hormone therapy begin treatment with anti-resorptive agents?
- **Key Question 3:** For how long should a patient undergoing adjuvant hormone therapy be treated with BMAs to prevent fractures from CTIBL?
- **Key Question 4:** Is there a role for adjuvant BMAs in improving survival outcomes for EBC patients?

Updated overview on AIOM key questions and recommendations

Key Question 1: In women with EBC undergoing adjuvant hormone therapy, which drugs should be used to reduce the risk of fractures in CTIBL?

Recommendation 1. *In women with BC undergoing adjuvant hormone therapy with aromatase inhibitors (+/- GnRH analogue), denosumab 60 mg/each six months should be considered for the prevention of CTIBL fractures.*

- Certainty of evidence: moderate
- Strength of recommendation: strong in favor (as per the GRADE framework)

Clinical interpretation 1. Several trials, meta-analyses, and studies demonstrate that BMAs, such as denosumab and BPs, effectively prevent CTIBL in EBC patients receiving adjuvant AIs with or without GnRH analogues.[19] Conversely, this does not apply to TAM, which affects bone differently and depending on menopausal status. Indeed, in a cohort of 5 million EBC patients treated with TAM, Kyvernitakis et al. reported a higher fracture incidence among women aged 18–50 (6.3% vs. 3.6%; HR 1.75, 95% CI 1.25–2.48) compared to no significant difference in those aged 55–90 (10.1% vs. 9.3%; HR 0.97, 95% CI

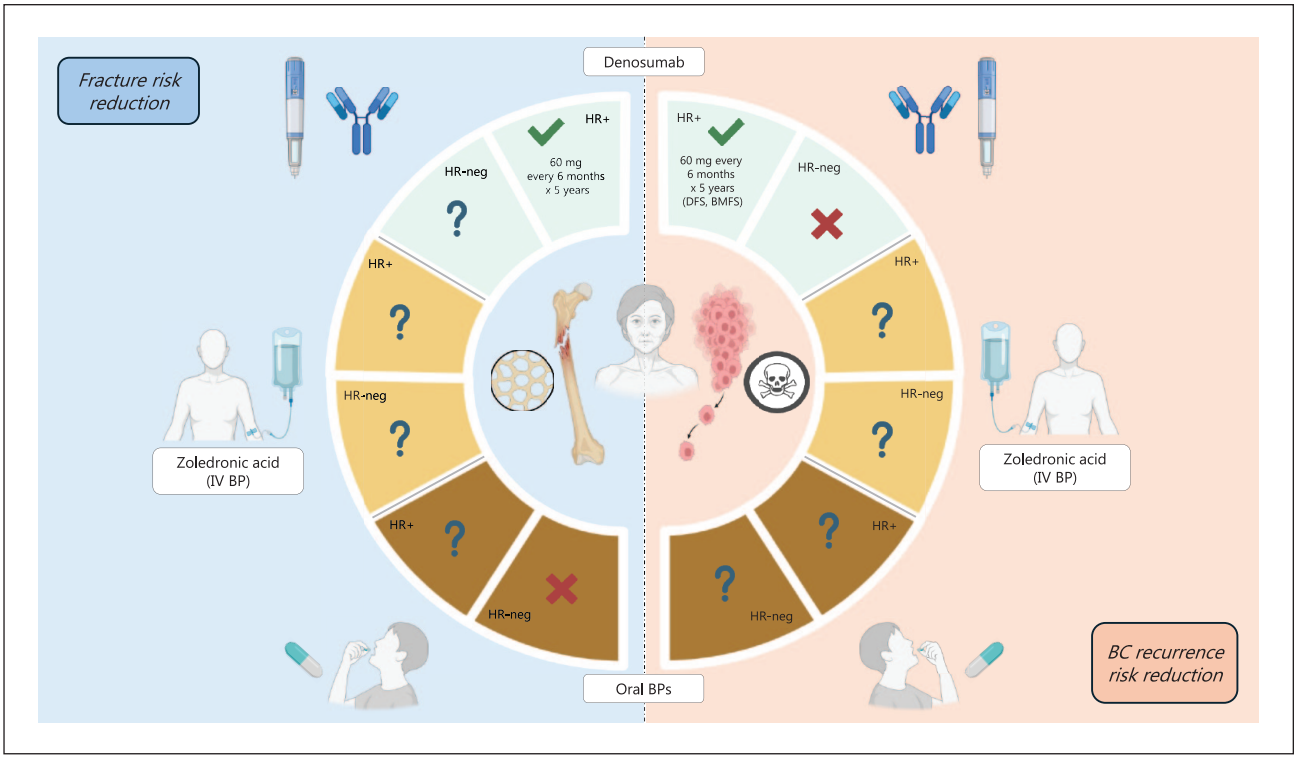

Figure 1. Visual summary of current evidence on the impact of each class of BMAs on bone health and survival outcomes, stratified by breast cancer HR status in post-menopausal patients, including those with treatment-induced (iatrogenic) menopause such as pre-menopausal women receiving ovarian suppression.
✔= indicates the presence of randomized trials or robust prospective direct evidence demonstrating a significant benefit in terms of either recurrence risk reduction or bone health improvement, specifically within the considered subgroup (defined by menopausal and receptor status).
?= indicates indirect (not specific to the subgroup), inconclusive evidence or derived from retrospective studies, non–pre-specified subgroup analyses, or meta-analyses.
✖= indicates a lack of evidence supporting any benefit for the given subgroup and outcome.
* Both "low-dose" zoledronate (4 mg every six months for three years) and "high-dose" regimens (4 mg IV every three to four weeks for 6 doses, then every three months for 8 doses, followed by every six months for 5 doses)
Breast Cancer (BC), Intravenous (IV), Bisphosphonates (BPs), Hormone Receptor–Negative (HR-neg), Hormone Receptor–Positive (HR+), Disease-Free Survival (DFS), Bone Metastasis–Free Survival (BMFS).
Illustrations were created by the authors using bioRender (https://www.biorender.com) and Microsoft PowerPoint.

0.81–1.16).[20] This paradox may be explained considering that in post-menopausal women, when estradiol levels are very low, TAM acts as an estrogen agonist in bone offering protective effects, while in pre-menopausal women, it may elicit an opposite impact by competing with the stronger estradiol for HR binding. Furthermore, in pre-menopausal women, TAM, with or without GnRH analogues, seems less detrimental to bone than AIs combined with GnRH analogues.[21] Therefore, standalone TAM does not necessitate BMAs for skeletal protection in post-menopausal women, while in pre-menopausal EBC patients, evidence for their benefit is limited and indirect.[3] A visual summary of current evidence on the impact of each class of BMAs on bone health, stratified by menopausal and HR status, is presented in **Figure 1** and **Figure 2.**

"ABCSG-18", a large double-blind phase III trial, randomized 3425 postmenopausal HR+ EBC patients on adjuvant AI to receive denosumab at the osteoporotic dosage (60 mg subcutaneously every six months for five years) or placebo, with time to first clinical fracture as the primary endpoint.[22] After 11 years from randomization, a maintained, albeit reduced, bone protection with denosumab was reported either in terms of preserved BMD at the lumbar spine, total hip, and femoral neck and especially in terms of reduced fracture incidence (HR 0.76; 95% CI, 0.63 to 0.92; overall rates 15.9% vs 19.2%).[11] These positive results were also confirmed by the other large phase III randomized trial, the "D-CARE", which randomized 4509 patients to receive placebo or a more intensive schedule (120 mg subcutaneously every three to four weeks for approximately six months, then every 12 weeks for a total duration of five years).[23] It enrolled both pre- and post-menopausal patients and HR+/negative subtypes. Nearly all received (neo)adjuvant chemotherapy along with anti-HER2 therapy and ET accordingly to specific subtype. Also, in this case the time to first on-study fracture, evaluated as a prespecified exploratory endpoint, favored the denosumab group (HR 0.76 95% CI

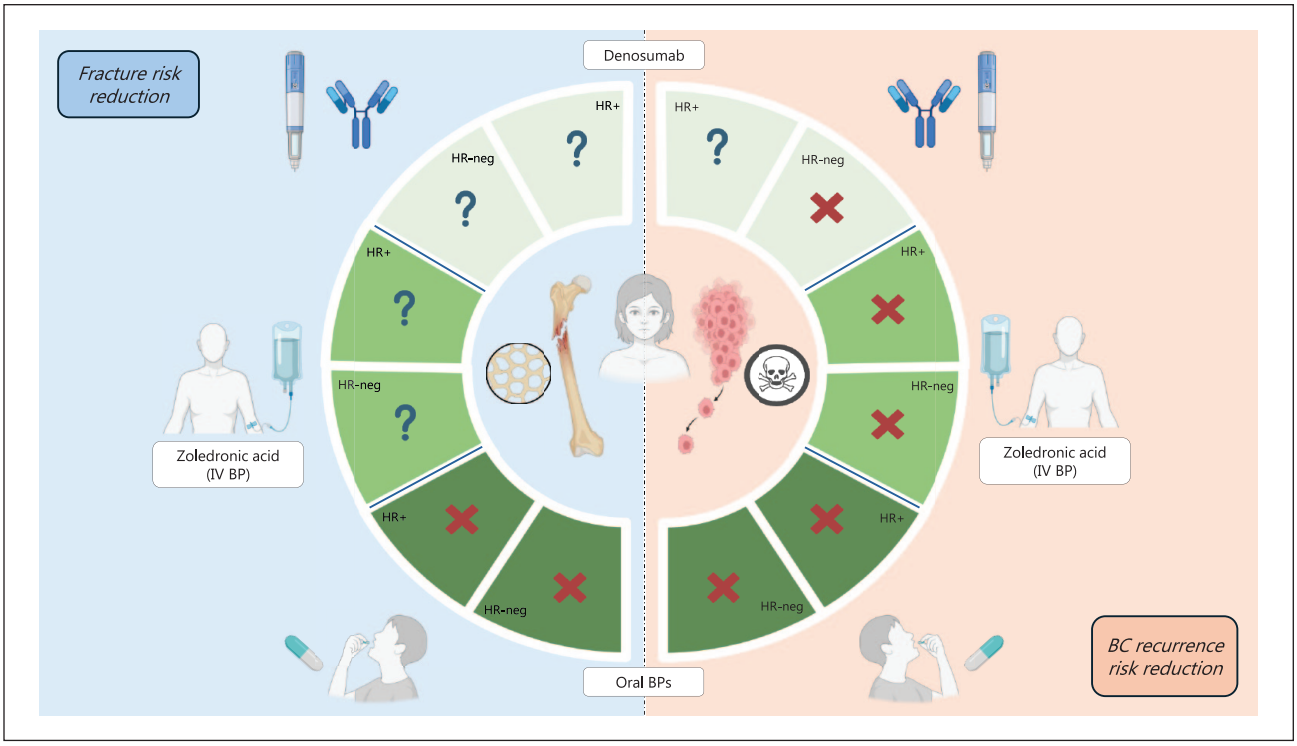

Figure 2. Visual summary of current evidence on the impact of each class of BMAs on bone health and survival outcomes, stratified by breast cancer HR status in pre-menopausal patients, excluding those receiving ovarian suppression.
✔= indicates the presence of randomized trials or robust prospective direct evidence demonstrating a significant benefit in terms of either recurrence risk reduction or bone health improvement, specifically within the considered subgroup (defined by menopausal and receptor status).
?= indicates indirect (not specific to the subgroup), inconclusive evidence or derived from retrospective studies, non–pre-specified subgroup analyses, or meta-analyses.
✖= indicates a lack of evidence supporting any benefit for the given subgroup and outcome.
Breast Cancer (BC), Intravenous (IV), Bisphosphonates (BPs), Hormone Receptor–Negative (HR-neg), Hormone Receptor–Positive (HR+).
Illustrations were created by the authors using bioRender (https://www.biorender.com) and Microsoft PowerPoint.

0.63–0.92) regardless of menopausal status.[24] Recently, Mastrantoni et al. conducted an intriguing meta-analysis combining data from these two large trials.[13] Regardless of menopausal status, it confirmed a statistically significant reduction in the time to the first fracture (HR 0.76; 95% CI 0.67–0.87) and a reduction in fracture incidence (relative risk [RR] 0.79; 95% CI 0.70–0.89) with five years of denosumab treatment compared to placebo (at 72 months follow-up, 10.7% vs. 14.2% with placebo).[13] A recent small randomized controlled trial, specifically enrolling pre-menopausal HR+ patients (N=68) undergoing adjuvant AI and GnRH analogue, confirming that "low-dose" denosumab effectively preserved BMD, bone microarchitecture, and estimated bone strength in this setting, likely improving fracture-free survival.[17]

On the other hand, among BPs, ZOL has the most extensive and consistent evidence of skeletal protection in both pre- and post-menopausal settings.[3,4,25] However, ZOL's primary benefit lies in improving and preserving BMD.[26-29] However, the latter is a main predictive factor for fracture and therefore a surrogate endpoint for their prevention only in an osteoporosis setting.[30] Indeed, the pathophysiology underlying CTIBL in EBC patients undergoing adjuvant ET, differs from that of primary and postmenopausal osteoporosis, with a prevalent role for bone quality alterations rather than quantity.[30] For example, some evidence suggests that fat body mass may be another independent predictive factor associated with fragility fractures in this setting. Therefore, a comprehensive osteo-sarcopenic obesity evaluation could be considered as a more reliable predictor of skeletal complications, beyond a BMD-centered approach.[31-33] Moreover, direct evidence from large randomized trials on fracture risk reduction with ZOL is limited, being mostly evaluated as a secondary endpoint. For example, the phase III "AZURE" trial randomized both HR+/HR- and pre- and post-menopausal EBC patients to receive ZOL or placebo in addition to standard (neo)adjuvant therapy (chemotherapy and/or ET, both TAM and/or AIs without ovarian suppression).[28,34] It demonstrated a reduction of the five-year fracture rate (5.9% [95% CI 4.8–7.1%] vs 3.8% [95% CI 2.9–4.7%]), regardless of menopausal status, in both HR+ (control 9.16% vs. ZOL 6.71%) and HR- disease (control 6.36% vs. ZOL 4.35%) and a significant delay in the time to the

first fracture (HR 0.69, 95% CI 0.53–0.90).[34] However, it should be noted that most of the fracture prevention benefit was observed after a DFS event (HR 0.3; 95% CI 0.17–0.53) and skeletal outcomes were evaluated as secondary endpoint. Moreover, the intensive "high-dose" regimen employed in this trial (4 mg IV every three to four weeks for 6 doses, followed by every three months for 8 doses, and then every six months for 5 doses) differ from the "low dose" used routinely in the osteoporotic setting. Nevertheless, real-world evidence supports ZOL's protective effect at the osteoporotic "low dose" (5 mg IV every 12 months) against vertebral fractures in both pre- (although examined in conjunction with oral BPs) and post-menopausal EBC patients undergoing AIs.[32,35]

Similarly, data on the use of orally administered BPs (such as pamidronate, ibandronate, risedronate, and clodronate) show only modest effectiveness in increasing BMD at the lumbar spine and maintaining it at the femoral head, with limited and indirect evidence for fracture prevention.[3] For instance, a large-scale observational study of 36,472 post-menopausal osteoporotic EBC patients receiving AIs and oral BPs indicated a 30% reduction in fractures over 10 years (HR 0.69, 95% CI 0.48–0.98).[36] Conversely, other real-world evidence shows no significant fracture risk reduction with oral BPs in post-menopausal EBC patients undergoing AI, whereas a benefit is observed in pre-menopausal patients (although evaluated including also ZOL).[32,35] A comprehensive meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which included 13,341 HR+/- pre- and post-menopausal EBC patients receiving BPs, reported a reduction in fracture rates (5.1% vs. 6.3% although also including IV agent).[37] Additionally, a recent network meta-analysis, including overall 34 trials with 33,793 EBC patients, observed that treatment with clodronate or ibandronate significantly decreased the number of fractures compared to no treatment or placebo (clodronate: RR 0.60, 95% CI 0.39–0.92; ibandronate: RR 0.57, 95% CI 0.38–0.86).[38] In the same direction, risedronate was found to probably reduce the number of fractures (RR 0.56, 95% CI 0.15–2.16), while pamidronate likely increased the number of fractures (RR 1.52, 95% CI 0.75–3.06), though with moderate certainty. Interestingly, in contrast with the existing literature, the same network meta-analysis seems to downplay the protective role of denosumab and ZOL, since the authors observed only a likely slight reduction in the number of fractures with these agents (RR 0.73, 95% CI 0.52–1.01 and RR 0.79, 95% CI 0.56–1.11 respectively).

In the EBC setting, it remains unclear which of the two drug classes offers greater benefit, as no head-to-head comparison exists. However, even at the osteoporotic 'low dose,' denosumab has stronger evidence for fracture risk reduction, supported by large randomized controlled trials with long-follow up period, compared to BPs, particularly oral formulations, evaluated in smaller cohorts with inconsistent and limited results. Therefore, for the prevention and management of CTIBL, denosumab 60 mg every six months is consistently considered a valid option across various international guidelines.[6–9] Unlike the Italian recommendation and associated reimbursement criteria, which restrict its use solely to bone protection, other guidelines tend to prioritize BPs, particularly in patients at higher risk of relapse, acknowledging their potential role in metastasis prevention (as discussed further).[6,7]

Key Question 2: When should patients affected by EBC who are starting adjuvant hormone therapy begin treatment with anti-resorptive agents?

Recommendation 2. *For patients with EBC receiving adjuvant aromatase inhibitor (+/-* GnRH analogues), *BMAs should be taken into consideration from the start of hormone therapy itself (primary prevention of CTIBL).*

- Certainty of evidence: moderate
- Strength of recommendation: strong in favor (as per the GRADE framework)

Clinical interpretation 2. The optimal timing for initiating BMAs for primary fracture prevention is not consistently defined internationally. Evidence from the ABCSG-18 trial shows that "low-dose" denosumab significantly reduces the incidence of clinical fractures across all patient subgroups, regardless of initial T-score or whether treatment began concurrently with or after adjuvant ET.[22] Moreover, considering BPs, initiating early ZOL at "low-dose" (4 mg IV every six months for a total of five years) significantly improves and maintains BMD throughout the treatment period in comparison with delayed administration (when is observed T-score of -2 or lower, or after a fracture event). Specifically, three dedicated randomized controlled trials consistently demonstrated a statistically significant increase in BMD (primary endpoint) with upfront "low-dose" ZOL compared to deferred administration in postmenopausal HR+ women receiving AIs. The mean BMD differences at the lumbar spine in favor of early treatment were 8.9% in "Z-FAST" (n=602, at 5 years), 9.7% in "ZO-FAST" (n=1605, at 5 years), and 5.43% in "E-ZO-FAST" (n=527, at 12 months) trials.[26-28] However, a statistically significant reduction in bone fractures was not observed, although they were not powered to evaluate this endpoint.[26] Interestingly, a mixed treatment analysis of randomized studies evaluating immediate denosumab or ZOL versus delayed treatment for post-menopausal EBC patients treated with AIs observed that, at the 36-month, the risk of fractures was reduced with immediate denosumab compared to delayed treatment (OR: 0.50,

95% CI 0.33-0.75) while it was not decreased for immediate ZOL versus delayed (OR: 0.91, 95% CI 0.56-1.44).[39] Overall, the absence of validated T-score thresholds (either at baseline or during follow-up) for initiating BMA treatment, the proven BMD benefits with upfront use (despite its uncertain role as a surrogate for fracture risk), the rapid bone loss induced by adjuvant ET, and the high prevalence of osteoporosis and fracture risk factors in EBC patients, all support initiating BMAs at the start of adjuvant ET.[8,9] On the other hand, European and American guidelines recommend early initiation of BMAs (specifically BPs) alongside other adjuvant treatments, however with a primary focus on reducing disease recurrence rather than maximizing bone protection.[6,7]

Key Question 3: For how long should a patient affected by EBC undergoing adjuvant hormone therapy be treated with BMAs to prevent fractures from CTIBL?

Recommendation 3. *BMAs can be taken into consideration for the entire duration of aromatase inhibitor (+/- GnRH analogues).*

- Certainty of evidence: moderate
- Strength of recommendation: moderate in favor (as per the GRADE framework)

Clinical interpretation 3. The optimal duration of BMAs treatment in EBC remains uncertain. It is generally recommended to continue anti-resorptive therapy for at least the duration of ET, since studies on AIs indicate that after discontinuation, the number of fractures appears to decrease and bone mass seems to partially recover.[8,9] Nevertheless, the evidence supporting this recommendation is indirect, and there are concerns about prolonged BMAs use due to the cumulative risk of adverse events (AEs) and increased costs, particularly in patients requiring "extended" ET. At the same time, discontinuation of BMAs also raises additional concerns. Notably BPs, typically accumulating in bone matrix during treatment, have a prolonged duration of action and lasting effect even after treatment discontinuation. The sustained skeletal protection is reflected in preserved BMD and reduced bone turnover markers, though its impact on fracture risk remains unknown.[15] On the other hand, discontinuing denosumab, owing to its distinct pharmacokinetic properties, is associated with a "rebound" increase in bone turnover that exceeds pretreatment levels in most patients, occasionally also resulting in multiple vertebral fractures.[40] The European Calcified Tissue Society (ECTS) working group performed an updated systematic review on this concerning topic, observing that specific evidence on "rebound" risk in EBC setting is limited.[40] A preliminary analysis of the "ABCSG-18" trial, presented in abstract form, reported that patients who discontinued "low-dose" denosumab had a significantly higher risk of developing clinical vertebral fractures (HR 2.44; 95% CI 1.12–5.32) and multiple vertebral fractures (HR 3.52; 95% CI 0.98–12.64) compared to those who stopped placebo.[41] However, this increased risk only occurred in patients who ended AI treatment prior to or $>$ 6 months after the last dose of denosumab administration, whereas no difference was seen in patients who ended AI treatment within six months of stopping denosumab. Reassuringly, the recent final protocol-defined analysis of the same trial, with 11-year follow-up, reported no increase in overall fracture risk (4.6% vs. 5.1% in the placebo group, 2.5 years after the last treatment administration), despite a higher number of multiple clinical vertebral fractures (14 vs 4).[11] Consistent with the notion that the timing of discontinuation could play a crucial role in the risk of rebound, a reported case series of 15 patients with EBC treated with AIs showed that 10 of the patients who experienced fragility vertebral fractures after stopping denosumab had discontinued it at the same time as ET.[42] Indirectly, considering the data from osteoporotic postmenopausal women setting, ESMO guidelines support initiating alternative anti-resorptive therapy (such as ZOL 4 or 5 mg) six months after the final denosumab dose to reduce or prevent this "rebound" effect.[6] Conversely, Italian guidelines recommend re-evaluating fracture risk and performing clinical and BMD-radiographic follow-up every 18 months after adjuvant ET completion, especially in those previously treated with denosumab, but provide no guidance on exact BMAs discontinuation timing or managing the possible "rebound" effect.

BMAs and EBC survival: Clinical perspectives and insights

Key Question 4: Is there a role for BMAs in improving survival outcomes for patients affected by EBC?

While BMAs are primarily used to improve bone health, they could potentially also reduce the risk of distant bone metastases, extra-osseous recurrences, and impact survival outcomes by modulating the tumor-bone microenvironment and exerting immunomodulatory effects.[43] However, their role remains uncertain on this point, with different trials often yielding conflicting results. A visual summary of current evidence on the impact of each class of BMAs on survival outcomes, stratified by menopausal and HR status, is presented in **Figure 1** and **Figure 2.**

For instance, denosumab has not consistently demonstrated a survival benefit in EBC setting. The contrasting results from two large randomized controlled trials[11,23] have been corroborated by the recent meta-analysis conducted

by Mastrantoni et al., which found no significant advantage with denosumab in terms of DFS (HR 0.93; 95% CI 0.74–1.16), neither BMFS (HR 0.89; 95% CI 0.75–1.07) or OS (HR 0.91; 95% CI 0.71–1.17) in the pooled population.[13] However, a statistically significant improvement was observed in BMFS (HR: 0.83; 95% CI: 0.71–0.97) and DFS (HR: 0.88; 95% CI: 0.78–0.99) in the HR+/HER2-negative patients, with also a borderline significant OS benefit (HR 0.83; 95% CI 0.79–1.00). At the same line, the final update from the "ABCSG-18" trial, confirmed a survival benefit with "low-dose" denosumab in HR+ postmenopausal patients: in terms of nine-year DFS (79.4% vs 75.9% HR 0.83; 95% CI, 0.71 to 0.97), BMFS (88.9% vs 86.4% HR 0.81; 95% CI, 0.65 to 1.00), non-BMFS (89.0% vs 86.5% HR 0.78; 95% CI, 0.63 to 0.96), all secondary endpoints of the trial.[11] Moreover, censoring for late crossover and use of other anti-resorptive agents a significant advantage in OS at nine years was also observed (91% vs. 89.5%, HR: 0.74; 95% CI, 0.58 to 0.94). Additionally, a particularly pronounced DFS advantage is reported when denosumab treatment begins at the start of ET (10% point difference in DFS). This apparent advantage in the HR+ population aligns with preclinical evidence showing that ET significantly alters bone turnover and receptor activator of nuclear factor kappa-B ligand (RANKL) release, potentially fostering the development and proliferation of bone micro-metastatic niches.[43] Consequently, targeted anti-RANKL therapies, like denosumab, may disrupt this mechanism in HR+ patients receiving ET, potentially preventing the initial occurrence of bone metastasis and subsequent extra-osseous dissemination. However, it should be also noted that the observed survival benefits in "ABCSG-18" trial, appear to be primarily driven by a reduction in second primary invasive cancers and deaths from any cause (composite endpoints), with no major differences for locoregional recurrences or distant metastases, including bone metastases. Moreover, the D-CARE trial failed to demonstrate a survival advantage in terms of either BMFS or DFS, irrespective of menopausal and HR status, despite its more intensive regimen.[23] One possible explanation could be both the inclusion of higher-risk and heterogeneous patients, that may underpin a different biological background (such as a various musculoaponeurotic fibrosarcoma oncogene homolog [MAF] status and RANK/RANKL expression levels). Moreover, as noted, denosumab's efficacy may rely on effective estrogen deprivation; notably, nearly 20% of patients in "D-CARE" trial were HR-, and about half were pre-menopausal without adequate ovarian suppression. Additionally, even if a direct dose–response effect does not appear to exist, why a lower dose might be more effective than the higher one tested in D-CARE is still unclear.[44] A possible explanation has been recently hypothesized: an excessive suppression of bone turnover could paradoxically create a hostile environment, potentially failing to reduce metastatic potential.[45]

Regarding BPs, the previously cited meta-analysis conducted by the EBCTCG[37] observed a statistically significant reduction in BMFS, DFS and BC mortality (3.3% reduction at 10 years, RR 0.82; 95% CI 0.73–0.93) for post-menopausal women (HR+/HR−negative) receiving BPs (excluding pamidronate, which showed no advantage, and with limited data for risedronate and alendronate). On the other hand, among premenopausal women, no apparent BPs protective effect on any survival outcome was observed. Another meta-analysis and systematic review by Sanaat et al. suggested a survival positive impact of BPs also in peri-menopausal BC survivors, reporting improved DFS (HR 0.89; 95% CI 0.83–0.97; p=0.005) and OS (HR 0.75; 95% CI 0.63–0.89).[46] Furthermore, a recently published meta-analysis by Mittal et al., which included 11 trials (with 24,023 patients) focusing on survival outcomes as primary endpoints and incorporating modern adjuvant chemotherapy regimens, though not stratified by menopausal or HR status, observed a five-year DFS benefit in those receiving BPs (both IV and oral) compared to the control group (84.8% vs. 82.1%; pooled HR 0.89; 95% CI 0.81–0.97).[16] However, this benefit did not translate into a statistically significant difference in five-year OS (92.1% vs. 90.9%; HR 0.92; 95% CI 0.83–1.03). Notably, BPs appear to have paradoxically a detrimental effect in higher-risk patients, such as those with N+ status, tumors larger than 3 cm, HR-negative status, or those who received taxane or anthracycline chemotherapy (DFS HR 0.95; 95% CI 0.80–1.12; OS HR 1.04; 95% CI 0.81–1.32).

Among BPs, ZOL has the most extensive data from phase III randomized control trials, although with some controversial evidence and without a clear OS benefit. In the "ABCSG-12" trial, after a median follow-up of 94.4 months, the addition of "low-dose" ZOL (4 mg every six months for three years) in HR+ pre-menopausal patients undergoing ET (TAM or AI) and GnRH analogue, significantly improved DFS (HR=0.77; 95% CI 0.60–0.99), regardless of ET received. A trend toward improved OS was also observed (HR = 0.66; 95% CI 0.43–1.02), with absolute risk reductions of 3.4% for DFS and 2.2% for OS.[47] Conversely, the recently published 10-year update of HOBOE phase III trial, at a median follow-up of 9.2 years, observed that in the same setting, pre-menopausal HR+ EBC receiving GnRH analogue, "low-dose" (5 mg every 12 months) of ZOL+AI (letrozole) improved DFS over TAM (HR = 0.58; 95% CI 0.41-0.82), although without any statistically significant difference in OS (global log-rank p= 0.103).[18] Notably, the pairwise DFS comparison between ZOL+AI and AI alone was not statistically significant, failing to cross the predefined Bonferroni-Holm threshold (p= 0.687). On the other hand, in post-menopausal setting, immediate "low-dose" (4 mg every six months for five years) ZOL administration in "ZO-FAST" trial reduced the risk of DFS events by 34% (HR= 0.66; p= 0.037) with fewer local (0.9% versus 2.3%) and distant (5.5% versus 7.7%) recurrences versus delayed

ZOL.[48] However, this finding was not confirmed in the "Z-FAST" trial with the same ZOL schedule, reporting comparable disease recurrence rates (upfront, 9.8% vs delayed 10.5%; p=0.62).[26] In the "AZURE" trial, "high-dose" ZOL improved distant DFS only in those who were over five years since menopause at trial entry regardless of HR status (adjusted HR 0.75, 95% CI 0.58–0.97), but without a significant OS benefit (0.81 95% CI 0.63–1.04).[28] Notably, the enrolled pre-menopausal patients that did not receive ovarian suppression per prevailing local treatment practices. Similarly, the phase III NeoAdjuvant Trial Add-oN ("NaTaN") study found only in those over 55 years of age a positive trend for DFS (HR 0.83 p=0.480) favoring "high-dose" ZOL (same schedule of AZURE) when added in HR+/- patients not achieving pathological complete response after neoadjuvant therapy.[49]

Regarding oral BPs, direct evidence of a survival benefit from phase III trials remains limited and conflicting. For instance, similarly to the previous "GAIN" trial, the recent "TEAM-IIB" phase III randomized study, at a median follow-up of 8.5 years, found that oral ibandronate 50 mg daily for three years did not improve DFS, BMFS, or OS in HR+ post-menopausal women undergoing ET.[50,51] However, both the EBCTCG meta-analysis and the SWOG S0307 phase III study found no significant differences in survival impact between ZOL, clodronate, and ibandronate, regardless of HR or menopausal status.[52] Evidence from the recent network meta-analysis by Adams et al., suggests that clodronate (HR 0.95, 95% CI 0.77–1.17) and ibandronate (HR 1.06, 95% CI 0.83–1.34), likely result in little to no difference in OS benefit compared to no treatment or placebo (low certainty), the same as for ZOL (HR 0.93, 95% CI 0.76–1.14) and denosumab (HR 0.91, 95% CI 0.69–1.21).[38] Furthermore, the effect of pamidronate (HR 1.20, 95% CI 0.81–1.78) on OS remains uncertain, with a potential detrimental effect compared to no treatment or placebo (very low certainty). Moreover, it remains unclear whether the treatment schedule, dose, and duration of BPs influence survival outcomes, as some studies (particularly those involving ZOL) suggest they may not have a significant impact [53]. Indeed, the Phase III "SUCCESS-A" trial randomized 3754 high-risk patients (N+ or N-negative with ⩾ pT2, G3, ER-negative, age ⩽35) to receive either a "short" two-year (4 mg IV every three months) or an "extended" five-year (4 mg IV every three months for two years, then every six months for three years) course of "intermediate dose" ZOL after adjuvant chemotherapy.[54] Irrespective of menopausal status, a two-year regimen of ZOL has been shown to be non-inferior to a five-year regimen in terms of DFS and OS. Additionally, the extended five-year treatment was however associated with a higher frequency of AEs compared to the two-year treatment (46.2% vs. 27.2%, p = 0.001; grade 3-4 adverse events: 7.6% vs. 5.1%, p = 0.006). Similarly, a recent exploratory analysis of the "ABCSG-12" phase III study, reported no statistically significant difference for DFS or OS in the patients who received ⩽6 ZOL infusions compared to those who received ⩾7 ZOL infusions.[12] Consistently, the EBCTCG meta-analysis revealed no significant difference in BMFS benefit based on the duration or dose of BPs treatment administered.[37] Finally, a recent study by Awan et al. randomized 211 post-menopausal EBC patients (15% HR-negative) to either a single infusion of ZOL 4 mg/IV or six-monthly treatment over three years.[14] After three years of follow-up, there were no significant differences between the two treatment arms in terms of quality of life, toxicity, relapse-free survival, BMFS and OS. Despite the trial is not powered for non-inferiority, longer-term follow-up is ongoing to confirm these findings.[14]

Despite the lack of direct randomized comparisons, a retrospective cohort study of 37,724 post-menopausal EBC patients (aged ⩾66), including both HR+ and HR– cases, revealed different survival outcomes between patients receiving denosumab or BPs. Among them, 7925 (21%) received at least six months of BMA at recommended osteoporosis doses within the first two years after diagnosis: of these 6898 (80.7%) received BPs only, 1204 (15.2%) received denosumab only, and 323 (4.1%) received both. At a median follow-up of 64 months, BPs use was associated with improved OS (HR 0.87; 95% CI 0.82–0.93) and breast-cancer specific survival (BCSS) (HR 0.77; 95% CI 0.64–0.92), whereas denosumab showed no survival benefit (OS HR 1.05 95% CI 0.90-1.22, BCSS HR 1.09 95% CI 0.66-1.82).[55]

In conclusion, the survival benefit of BMAs in EBC remains uncertain due to conflicting data, and further studies are needed to clarify their impact and especially identify the patients most likely to derive a benefit. Denosumab failed to demonstrate consistently a DFS and/or OS gain with some mixed results in selected patient subgroups (HR+ post-menopausal), while BPs, specially ZOL, have occasionally demonstrated DFS improvements in menopausal women (natural or induced), though findings have been contradictory and lacking direct OS benefit. Therefore, based on this evidence, Italian guidelines do not recommend or reimburse the use of BMAs to reduce BC recurrence risk. In contrast, while both ESMO and ASCO guidelines agree that denosumab lacks sufficient evidence for this purpose, they endorse BPs (ZOL or daily oral clodronate or ibandronate) in post-menopausal women (whether natural or induced) for metastasis prevention. However, the ESMO guidelines restrict this recommendation to patients at higher risk of relapse.

Overview of BMAS safety profile in EBC setting

Both BPs and denosumab are associated with specific and overlapping AEs, making it essential for physicians to

inform patients about potential risks and adopt proactive strategies to minimize their frequency and severity.

For instance, the most recent update of the "ABCSG-18" trial, which used a "low" anti-osteoporotic dosage, reassures on the long-term denosumab safety, reporting no cases of medication-related osteonecrosis of the jaw (MRONJ) and only one case each of hypocalcemia and atypical femoral fracture (AFF).[11] Conversely, a more intensive denosumab schedule in D-CARE trial was associated with a higher frequency of AEs, including 5.4% cases of MRONJ compared to 0.2% with placebo (RR 30.18; 95% CI 11.17–81.58), 0.4% cases of AFF versus none with placebo (RR 18.80; 95% CI 1.09–322.89), and 6.5% cases of hypocalcemia compared to 3.6% with placebo (RR 1.80; 95% CI 1.38–2.35).[23] Therefore, this schedule is not recommended by any guidelines, which instead favor the safer and less intensive 60 mg every six months regimen. Overall, the pooled toxicity data from the recent meta-analysis by Mastrantoni and colleagues, evidenced no significant differences between denosumab and placebo in AEs (RR 1.00; 95% CI 0.99–1.01), severe AEs (RR 1.01; 95% CI 0.95–1.08), or discontinuation rates (RR 1.03; 95% CI 0.63–1.68).[13] However, despite its favorable safety profile, as previously mentioned, denosumab discontinuation is associated with a "rebound" phenomenon that is poorly characterized in the EBC setting, seemingly influenced by the timing of interruption relative to ET completion and, in some cases, leading to multiple vertebral fractures. Further research and clear guidance on its management and strategies to mitigate this adverse consequence remain necessary.

Similarly, BPs are usually well tolerated, without serious side effects.[6,56] For IV BPs, the main AE is an acute-phase reaction within the first three days: flu-like symptoms that usually resolve but may last up to 14 days. On the other hand, oral BPs can cause irritative effects on gastrointestinal mucosa resulting in esophagitis, dysphagia, and gastric ulcers but also nausea, vomiting, abdominal pain, and diarrhea. Considering both oral and IV BPs, a well-known complication is the hypocalcemia, despite being rarely reported (0.5%).[16] Another rare side effect is renal toxicity (e.g., acute tubular necrosis), mainly occurring in patients with chronic kidney disease.[57] The recent meta-analysis by Mittal et al. confirmed an overall low incidence of any grade renal toxicity (0,15% 95% CI 0.07–0.24).[16] As with denosumab, other rare but severe complication, are AFFs and particularly MRONJ.[58] The absolute risk of AFFs in patients receiving BPs (and denosumab) is low, ranging from 3.2 to 50 cases per 100,000 person-years, though long-term use may increase this risk to approximately 100 cases per 100,000 person-years.[59] Moreover, a network meta-analysis conducted by Adams et al., reports that ibandronate and ZOL probably increases the occurrence of MRONJ (moderate certainty) compared to no treatment/placebo, while clodronate (RR 2.65, 95% CI 0.83 to 8.50) may increase this risk of MRONJ (low certainty).[38] However, the literature data about MRONJ is partially conditioned by a controversial and debated definition of the disease, based only on clinical signs and inducing underestimation.[60-62] Furthermore, most randomized trials showed limits (e.g., accrual of "favorable" patients and limited follow-up) in comparison with real life reports. Even with these bias, the risk for MRONJ appears to be increased with higher dose density, prolonged treatment duration and IV administration. In the "SWOG S0307" trial, which randomized patients to receive clodronate (1600 mg daily), ibandronate (50 mg daily), or "moderate-dose" ZOL (4 mg monthly for six months, then every three months) the incidence of MRONJ (assessed with a restricted definition) was indeed greater in patients receiving ZOL compared to other oral BPs (1.26% with ZOL vs. 0.77% with ibandronate and 0.36% with clodronate; Fisher's exact test p= 0.003).[52,63] Similarly, the meta-analysis by Mittal et al. reported an higher frequency of MRONJ in patients treated with ZOL at "moderate" dose compared to overall BPs (1%, 95% CI 0.75–1.15 vs 0.78% 95% CI 0.6–0.87).[16] Moreover, as for denosumab, BPs use at osteoporotic "low-dose" is associated with a low incidence of MRONJ (0-1% with IV and 0–0.5% with oral BPs).

Therefore, given that BMAs for EBC patients are recommended and reimbursed in Italy at osteoporotic "low doses," the incidence of AEs is expected to be generally low, resulting in good overall tolerability. Consequently, less stringent preventive measures for MRONJ are considered appropriate, as acknowledged by the Expert Panel of the Italian Societies of Oral Pathology and Medicine (SIPMO) and Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS).[64–66]

Conclusion

While the benefits of adjuvant BMAs in preserving bone health are well-established, their impact on survival outcomes in EBC remains an area of ongoing investigation and debate. Conflicting results in the literature, partly due to the high heterogeneity among trials and enrolled populations, ranging from HR+/HR-negative to pre- and post-menopausal women, underscore the need for a deeper understanding of the mechanisms driving BMAs' benefits. By identifying predictive factors, an enhanced patient selection could minimize toxicities and reduce financial burdens. Given the overlap between bone health management and bone metastasis prevention, holistic care through the collaboration of BC dedicated oncologists and osteo-oncology specialists is essential.[67] In conclusion, further guidance is needed to clearly define the role of BMAs in the rapidly changing and evolving adjuvant treatment landscape for EBC.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: L. Arecco: travel grant from AstraZeneca; research grant to the institution from Gilead. F. Miglietta: personal fees from Roche, Novartis, Pfizer/Seagen, MSD, Astrazeneca, Daiichi Sankyo, Menarini Stemline, Gilead. L. Del Mastro: Grants or contracts from Eli lilly; Novartis; Roche; Daiichi Sankyo; Seagen; Astrazeneca; Gilead; Pierre Fabre; Pfizer. Consulting fees: Eli lilly; Gilead; Daiichi Sankyio; Menarini Stemline; Novartis; Olema; Astrazeneca; MSD; Pfizer. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events Roche – Novartis - Pfizer – Eli lilly – Astrazeneca – MSD – Seagen – Gilead – Pierre Fabre – Eisai – Exact sciences – Ipsen – GSK – Agendia - Menarini Stemline. Support for attending meetings and/or travel: Roche – Daiichi Sankyo – Astrazeneca – Gilead – Menarini Stemline. Participation on a Data Safety Monitoring Board or Advisory Board Novartis – Roche – Eli Lilly – Pfizer – Daiichi Sakyo – Exact sciences – Gilead – Pierre Fabre – Eisai – Astrazeneca -Agendia – GSK -Seagen – MSD – Olema. T. Ibrahim (last 2 years): Fee for consultant (Pharmamar and Ipsen) and for speaker's bureau (Istituto Gentili). L. Biganzoli: Personal financial interests (Honoraria, consultancy or advisory role): Amgen, Institutional financial interests: Novartis. M. Di Maio: Honoraria for consultancy or participation to advisory boards from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, GlaxoSmithKline, Amgen, Merck, Takeda, Viatris, Ipsen, Astellas; institutional funding for work in clinical trials/contracted research from Beigene, Exelixis, MSD, Pfizer and Roche; AIOM president elect. J. Foglietta: personal fees from Pfizer/Seagen, Astrazeneca, Daiichi Sankyo, Menarini Stemline. L. Cortesi: Grants:Astra Zeneca, MSD, Pfizer; Consulting fees: Astra Zeneca, MSD, Pfizer, Novartis, Gilead, Roche, Daichii-Sankyo; Advisory Board:Astrazeneca, MSD, Daichii-Sankyo. L. Fortunato: Advisory Board MSD.

All other authors: no recent (last 2 years) declarations related with this paper.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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References

1. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2024; 35: P159-182.
2. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, *CA: Cancer J Clinicians* 2022; 721: 7–33.
3. Waqas K, Lima Ferreira J, Tsourdi E, et al. Updated guidance on the management of cancer treatment-induced bone loss CTIBL. in pre- and postmenopausal women with early-stage breast cancer. *J Bone Oncol* 2021; 28: 100355.
4. de Sire A, Lippi L, Venetis K, et al. Efficacy of antiresorptive drugs on bone mineral density in post-menopausal women with early breast cancer receiving adjuvant aromatase inhibitors: a systematic review of randomized controlled trials. *Front Oncol* 2022; 11: 829875
5. Shah R and O'Regan RM. Adjuvant endocrine therapy. In: Gradishar W (ed.) *Optimizing Breast Cancer Management. Cancer Treatment and Research*. Springer, 15-29.
6. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* 2020; 3112: 1650–1663.
7. Eisen A, Somerfield MR, Accordino MK, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH CCO. Guideline Update. *J Clin Oncol* 2022; 407: 787–800.
8. AssociazioneItalianadiOncologiaMedica(AIOM).Lineeguida carcinoma mammario in stadio precoce. *Istituto Superiore di Sanità; 2023*. https://www.iss.it/documents/20126/8403839/LG_C0013_AIOM_Ca-mammario-precoce.pdf/fb5df1bd-2712-9166-68e7-6e296912776e?t=1704702928747 (accessed 18 August 2025).
9. Associazione Italiana di Oncologia Medica (AIOM). Linee guida metastasi ossee e salute dell'osso. *Istituto Superiore di Sanità; 2024*. https://www.iss.it/documents/20126/8403839/LG_C0020_AIOM_Metastasi+ossee.pdf/25b94932-a5c4-2595-044f-bb149134b8c6?t=1716801199464 (accessed 18 August 2025).
10. Associazione Italiana di Oncologia Medica (AIOM). *Manuale metodologico per la produzione delle linee guida AIOM. AIOM; 2019*. https://www.aiom.it/wp-content/uploads/2019/01/LG_AIOM_2019_manuale_metodologico.pdf (accessed 18 August 2025).
11. Gnant M, Frantal S, Pfeiler G, et al. Long-term outcomes of adjuvant denosumab in breast cancer. *NEJM Evidence 2022*; 1(12).
12. Beltran-Bless AA, Clemons MJ, Fesl C, et al. Does the number of 6-monthly adjuvant zoledronate infusions received affect treatment efficacy for early breast cancer? A substudy of ABCSG-12. *Eur J Cancer* 2023; 180: 108–116.
13. Mastrantoni L, Garufi G, di Monte E, et al. Adjuvant denosumab in early breast cancer: a systematic review and meta-analysis of randomized controlled clinical trials. *Therap Adv Med Oncol* 2023; 15: 175883592311731.
14. Awan AA, Stober C, Pond GR, et al. A randomised trial comparing 6-monthly adjuvant zoledronate with a single one-time dose in patients with early breast cancer. *Breast Cancer Res Treat* 2024; 208: 523–533.
15. Brown J, Paggiosi MA, Rathbone E, et al. Prolonged bone health benefits for breast cancer patients following adjuvant

bisphosphonate therapy: the BoHFAB study. *J Bone Min Res* 2024; 391: 8–16.
16. Mittal A, Tamimi F, Molto C, et al. Benefit of adjuvant bisphosphonates in early breast cancer treated with contemporary systemic therapy: A meta-analysis of randomized control trials. *Heliyon* 2024; 102: e24793.
17. Ramchand SK, Ghasem-Zadeh A, Hoermann R, et al. Denosumab prevents bone loss and microarchitectural deterioration in premenopausal women with breast cancer receiving estradiol suppression therapy: a randomized controlled trial. *J Clin Oncol* 2024: 42: https://doi.org/10.1200/JCO.23.02309
18. Gravina A, Gargiulo P, de Laurentiis M, et al. Ten-year update of HOBOE phase III trial comparing triptorelin plus either tamoxifen or letrozole or zoledronic acid + letrozole in premenopausal hormone receptor-positive early breast cancer patients. *ESMO Open* 2025; 101: 104085.
19. Lambertini M, Arecco L, Woodard TL, et al. Advances in the management of menopausal symptoms, fertility preservation, and bone health for women with breast cancer on endocrine therapy. *Am Soc Clin Oncol Ed Book* 2023; 43: e390442.
20. Kyvernitakis I, Kostev K and Hadji P. The tamoxifen paradox—influence of adjuvant tamoxifen on fracture risk in pre- and postmenopausal women with breast cancer. *Osteoporosis Inter* 2018; 2911: 2557–2564.
21. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *New Eng J Med* 2018; 3792: 122–137.
22. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer ABCSG-18.: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 3869992: 433–443.
23. Coleman R, Finkelstein DM, Barrios C, et al. Adjuvant denosumab in early breast cancer D-CARE.: an international, multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2020; 211: 60–72.
24. Coleman R, Zhou Y, Jandial D, et al. Bone health outcomes from the international, multicenter, randomized, phase 3, placebo-controlled D-CARE study assessing adjuvant denosumab in early breast cancer. *Adv Therapy* 2021; 388: 4569–4580.
25. Kyvernitakis I, Kann PH, Thomasius F, et al. Prevention of breast cancer treatment-induced bone loss in premenopausal women treated with zoledronic acid: Final 5-year results from the randomized, double-blind, placebo-controlled ProBONE II trial. *Bone* 2018; 114: 109–115.
26. Kyvernitakis I, Kann PH, Thomasius F, et al. Final 5-year results of Z-FAST trial. *Cancer* 2012; 1185: 1192–1201.
27. Llombart A, Frassoldati A, Paija O, et al. Immediate administration of zoledronic acid reduces aromatase inhibitor–associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. *Clin Breast Cancer* 2012; 121: 40–48.
28. Coleman R, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE BIG 01/04. Randomised open-label phase 3 trial. *Lancet Oncol* 2014; 159: 997–1006.
29. Baek HS, shin K, Kim J, et al. Efficacy of a single 5 mg zoledronic acid infusion in preventing bone loss and fracture in postmenopausal women with breast cancer. *J Bone Min Metab* 2024; 426: 720–727.
30. 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; 2510: 1141–1152.
31. Pedersini R, Amoroso V, Maffezzoni F, et al. Association of fat body mass with vertebral fractures in postmenopausal women with early breast cancer undergoing adjuvant aromatase inhibitor therapy. *JAMA Network Open* 2019; 29: e1911080.
32. Birtolo MF, Pedersini R, Palermo A, et al. Bone-active drugs in premenopausal women with breast cancer under hormone-deprivation therapies. *Eur J Endocrinol* 2024; 1912: 117–125.
33. Cosentini D, Pedersini R, di Mauro P, et al. Fat body mass and vertebral fracture progression in women with breast cancer. *JAMA Network Open* 2024; 71: e2350950.
34. Wilson C, Bell R, Hinsley S, et al. Adjuvant zoledronic acid reduces fractures in breast cancer patients; an AZURE BIG 01/04 study. *Eur J Cancer* 2018; 94: 70–78.
35. Mazziotti G, Pedersini R, Vena W, et al. Real-world effectiveness of denosumab and bisphosphonates on risk of vertebral fractures in women with breast cancer undergoing treatment with aromatase inhibitors. *Calcified Tissue Inter* 2022; 1115: 466–474.
36. Pineda-Moncusí M, Garcia-Giralt N, Diez-Perez A, et al. Increased fracture risk in women treated with aromatase inhibitors versus tamoxifen: beneficial effect of bisphosphonates. *J Bone Min Res* 2020; 352: 291–297.
37. Early Breast Cancer Trialists Collaborative Groups EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015; 38610001: 1353–1361.
38. Adams A, Jakob T, Huth A, et al. Bone-modifying agents for reducing bone loss in women with early and locally advanced breast cancer: a network meta-analysis. *Cochrane Database System Rev* 2024; 2024(7).
39. Abdel-Rahman O. Denosumab versus zoledronic acid to prevent aromatase inhibitors-associated fractures in postmenopausal early breast cancer; a mixed treatment meta-analysis. *Exp Rev Anticancer Therapy* 2016: 168; 885–891.
40. 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 Metabol* 2021; 1061: 264–281.
41. Pfeiler G, SGG, ED, et al. Fracture risk after stopping adjuvant denosumab in hormone receptor positive breast cancer patients on aromatase inhibitor therapy - an analysis of 3,425 postmenopausal patients in the phase III ABCSG-18 trial. *J Bone Min Res* 2018; 33: 55.
42. Gonzalez-Rodriguez E, Aubry-Rozier B, Stoll D, et al. 2020. Sixty spontaneous vertebral fractures after denosumab discontinuation in 15 women with early-stage breast cancer under aromatase inhibitors. *Breast Cancer Res Treat* 2020; 1791: 153–159.
43. de Leon-Oliva D, Barrena-Blázquez S, Jiménez-Álvarez L, et al. The RANK–RANKL–OPG System: A multifaceted regulator of homeostasis, immunity, and cancer. *Medicina* 2023; 5910: 1752.

44. Perrone F and Gravina A. Denosumab in early breast cancer: negative data and a call to action. *Lancet Oncol* 2020; 211: 5–6.
45. Moretti L, Richelmi L, Cosentini D, et al. Adjuvant denosumab for early breast cancer–Evidence and controversy. *Breast* 2024; 78: 103826.
46. Sanaat Z, Nouri O, Khanzadeh M, et al. Bisphosphonates and prevention of the perimenopausal breast cancer recurrence: a systematic review and meta-analysis. *J Breast Cancer* 2022; 256: 454.
47. Gnant M, Mlineritsch B, Stoeger H, et al. 2015. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol* 2015; 262: 313–320.
48. Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid zoledronate. for postmenopausal women with early breast cancer receiving adjuvant letrozole ZO-FAST study: final 60-month results. *Ann Oncol* 2013; 242: 398–405.
49. von Minckwitz G, Rezai M, Tesch H, et al. 2016. Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer – The Phase III NeoAdjuvant Trial Add-oN NaTaN. study GBG 36/ABCSG 29. *Eur J Cancer* 2016; 64: 12–21.
50. von Minckwitz G, Möbus V, Schneeweiss A, et al. German adjuvant intergroup node-positive study: a phase iii trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer. *J Clin Oncol* 2013; 3128: 3531–3539.
51. Vliek SB, Noordhoek I, Meershoek-Klein Kranenbarg E, et al. Daily oral ibandronate with adjuvant endocrine therapy in postmenopausal women with estrogen receptor–positive breast cancer BOOG 2006-04: Randomized Phase III TEAM-IIB Trial. *J Clin Oncol* 2022; 4025: 2934–2945.
52. Gralow JR, Barlow WE, Paterson AHG, et al. Phase III randomized trial of bisphosphonates as adjuvant therapy in breast cancer: S0307. *JNCI* 2020: 1127: 698–707.
53. Amoroso V, Petrelli F, Pedersini R, et al. 2015. Adjuvant bisphosphonates in patients with breast cancer: does the potency matter? *Future Oncol* 2015; 1121: 2853–2856.
54. Amoroso V, Petrelli F, Pedersini R, et al. Prognosis of patients with early breast cancer receiving 5 years vs 2 years of adjuvant bisphosphonate treatment. *JAMA Oncol* 2021; 78: 1149.
55. Suarez-Almazor ME, Herrera R, Lei X, et al. Survival in older women with early stage breast cancer receiving low-dose bisphosphonates or denosumab. *Cancer* 2020; 12617: 3929–3938.
56. Goldvaser H and Amir E. Role of bisphosphonates in breast cancer therapy. *Curr Treat Opt Oncol* 2019; 204: 26.
57. Khan MI. 2023. Management of bone loss due to endocrine therapy during cancer treatment. *Osteoporosis Int* 2023; 344: 671–680.
58. Khow KSF, Shibu P, Yu SCY, et al. Epidemiology and postoperative outcomes of atypical femoral fractures in older adults: A systematic review. *J Nutrition Health Aging* 2017; 211: 83–91.
59. Black DM, Abrahamsen B, Bouxsein ML, et al. Atypical femur fractures: review of epidemiology, relationship to bisphosphonates, prevention, and clinical management. *Endocrine Rev* 2019; 402: 333–368.
60. Schiodt M, Otto S, Fedele S, et al. Workshop of European task force on medication-related osteonecrosis of the jaw: Current challenges. *Oral Diseases* 2019; 257: 1815–1821.
61. Bedogni A, Mauceri R, Fusco V, et al. Italian position paper SIPMO-SICMF on medication-related osteonecrosis of the jaw MRONJ. *Oral Diseases* 2024; 306: 3679–3709.
62. Campisi G, Bedogni A, Saia G, et al. Letter to editor regarding "bone modifying agents in breast cancer patients as adjuvant therapy and prevention of cancer treatment-induced bone loss (CTIBL): Evaluation of risk of medication-related osteonecrosis of the jaw (MRONJ). *Support Care Cancer* 2024; 3210: 698.
63. Kizub DA, Miao J, Schubert MM, et al. Risk factors for bisphosphonate-associated osteonecrosis of the jaw in the prospective randomized trial of adjuvant bisphosphonates for early-stage breast cancer SWOG 0307. *Support Care Cancer* 2021; 295: 2509–2517.
64. Yarom N, van Poznak CH, Epstein JB, et al. MASCC/ISOO Clinical Practice Statement: Adjuvant bone-modifying agents in primary breast cancer patients - prevention of medication-related osteonecrosis of the jaw. *Support Care Cancer* 2024; 328: 547.
65. Zhang X, Hamadeh IS, Song S, et al. Osteonecrosis of the Jaw in the United States Food and Drug Administrations Adverse Event Reporting System (FAERS). *J Bone Min Res* 2016; 312: 336–340.
66. Bertoldo F, Eller-Vainicher C, Fusco V, et al. Medication related osteonecrosis MRONJ. in the management of CTIBL in breast and prostate cancer patients. Joint report by SIPMO AND SIOMMMS, *J Bone Oncol* 2025; 50: 100656.
67. Recine F, et al. BOneHEalthManagEment in patients with early breast cancer: A Retrospective Italian osteoncology center "real-life" experience BOHEME Study. *J Clin Med 2019*; 811: 1894.