

**REVIEW ARTICLE**

# Assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy: Position statement of the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia

Mathis Grossmann<sup>1,2</sup>  | Sabashini K. Ramchand<sup>1,2</sup> | Frances Milat<sup>3,4,5</sup> |  
Amanda Vincent<sup>3,6</sup> | Elgene Lim<sup>7,8</sup> | Mark A. Kotowicz<sup>9,10,11</sup> | Jill Hicks<sup>12</sup> |  
Helena Teede<sup>3,6</sup> 

<sup>1</sup>Department of Endocrinology, Austin Health, Heidelberg, Vic., Australia

<sup>2</sup>Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Vic., Australia

<sup>3</sup>Department of Endocrinology, Monash Health, Clayton, Vic., Australia

<sup>4</sup>Hudson Institute of Medical Research, Clayton, Vic., Australia

<sup>5</sup>Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Vic., Australia

<sup>6</sup>Monash Centre for Health Research and Implementation, Monash Public Health and Preventative Medicine, Monash University, Clayton, Vic., Australia

<sup>7</sup>Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

<sup>8</sup>St Vincent's Hospital, University of New South Wales Sydney, Darlinghurst, NSW, Australia

<sup>9</sup>Deakin University, Geelong, Vic., Australia

<sup>10</sup>Department of Endocrinology and Diabetes, University Hospital, Geelong, Vic., Australia

<sup>11</sup>Department of Medicine, Melbourne Medical School – Western Campus, The University of Melbourne, St Albans, Vic., Australia

<sup>12</sup>Breast Cancer Network Australia, Camberwell, Vic., Australia

**Correspondence**

Mathis Grossmann, Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Vic., Australia.  
Email: mathisg@unimelb.edu.au

**Summary**

To formulate clinical consensus recommendations on bone health assessment and management of women with oestrogen receptor-positive early breast cancer receiving endocrine therapy, representatives appointed by relevant Australian Medical Societies used a systematic approach for adaptation of guidelines (ADAPTE) to derive an evidence-informed position statement addressing 5 key questions. Women receiving adjuvant aromatase inhibitors and the subset of premenopausal woman treated with tamoxifen have accelerated bone loss and increased fracture risk. Both bisphosphonates and denosumab prevent bone loss; additionally, denosumab has proven antifracture benefit. Women considering endocrine therapy need fracture risk assessment, including clinical risk factors, biochemistry and bone mineral density (BMD) measurement, with monitoring based on risk factors. Weight-bearing exercise, vitamin D and calcium sufficiency are recommended routinely. Antiresorptive

treatment should be considered in women with prevalent or incident clinical or morphometric fractures, a *T*-score (or *Z*-scores in women <50 years) of <-2.0 at any site, or if annual bone loss is ≥5%, considering baseline BMD and other fracture risk factors. Duration of antiresorptive treatment can be individualized based on absolute fracture risk. Relative to their skeletal benefits, risks of adverse events with antiresorptive treatments are low. Skeletal health should be considered in the decision-making process regarding choice and duration of endocrine therapy. Before and during endocrine therapy, skeletal health should be assessed regularly, optimized by nonpharmacological intervention and where indicated antiresorptive treatment, in an individualized, multidisciplinary approach. Clinical trials are needed to better delineate long-term fracture risks of adjuvant endocrine therapy and to determine the efficacy of interventions designed to minimize these risks.

#### KEYWORDS

bone density, early breast cancer, fracture, oestradiol deprivation

## 1 | INTRODUCTION

Adjuvant endocrine therapy improves oncologic outcomes in women with oestrogen receptor (ER)-positive early breast cancer. Consequent to the induced oestradiol depletion with aromatase inhibitors, bone loss is accelerated, which predisposes to increased fracture risk. In contrast, tamoxifen in postmenopausal women acts as an oestrogen on bone and retards bone resorption and reduces fracture risk. While there has been rapidly accumulating evidence on this topic, some evidence-based best practice knowledge gaps remain regarding the optimization of bone health in women with early breast cancer. Moreover, existing evidence may not always be adopted into clinical practice.

In this joint position statement, the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia review and adapt guidelines using a systematic approach to formulate clinical consensus recommendations on assessment and management of bone health in women with ER-positive breast cancer receiving endocrine therapy. We aim to address key gaps and to inform clinical management.

## 2 | BACKGROUND

Adjuvant endocrine therapies for ER-positive breast cancer include aromatase inhibitors (anastrozole, exemestane, letrozole) or selective oestrogen receptor modulators (SERM), usually tamoxifen. Aromatase inhibitors block the conversion of androgens to oestradiol. In postmenopausal women, this results in near complete (>98%) deprivation of circulating oestradiol. As aromatase inhibitors inhibit the oestradiol-mediated negative feedback on gonadotropin production, they cannot be used as breast cancer treatment

in premenopausal women unless ovarian function is suppressed, typically by pharmacological means (eg, gonadotropin-releasing hormone agonists) or by bilateral oophorectomy. SERMs act as ER antagonists in the breast but have partial agonistic activity in tissues such as bone and endometrium, and may be used in both pre- and postmenopausal women. Women who become menopausal during the course of their adjuvant therapy may switch from tamoxifen to an aromatase inhibitor.<sup>1</sup>

In postmenopausal women, aromatase inhibitors are preferred because of modest but significant improvements in breast cancer outcomes, including lower 10-year breast cancer mortality compared to tamoxifen (12.1% vs 14.2% relative risk [RR] 0.85; 95% confidence interval [CI] 0.75-0.96,  $P < .01$ ).<sup>2</sup> In premenopausal women, tamoxifen has traditionally been first-line treatment, although a combined analysis of 2 large randomized controlled trials (RCT), Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT), reported improved 5-year disease-free survival with ovarian suppression plus the aromatase inhibitor exemestane compared to ovarian suppression plus tamoxifen (91.1% vs 87.3%, hazard ratio [HR] 0.72; 95% CI 0.60-0.85;  $P < .001$ ).<sup>3</sup> The benefit was significant in premenopausal women with high-risk ER-positive, HER2-negative breast cancer, as defined by clinicopathological characteristics and in patients <35 years of age.<sup>4</sup>

Increasing the duration of endocrine therapy from 5 to 10 years can further reduce the risk of recurrence.<sup>5,6</sup> While the absolute benefit in reducing recurrence risk is modest, there has been no overall survival benefit with an extended adjuvant endocrine therapy approach reported to date. Further, extended treatment is associated with a significant increase in the incidence of adverse effects including endometrial cancer and venous thrombosis with tamoxifen, and osteoporosis and fracture risk with aromatase inhibitors. Compared to 5 years of aromatase inhibitor treatment followed by 5 years of placebo, 10 years of aromatase inhibitor

treatment significantly increased the incidence of osteoporosis (10% vs 7%,  $P = .02$ ) and of clinical fractures (133 vs 86,  $P = .001$ ), despite 50% of women in both groups receiving bisphosphonates during the study.<sup>6</sup> Whereas women receiving extended treatment had a mean total hip BMD loss of 3.2%, there was a 22.4% increase in women receiving placebo.

Due to earlier detection and advances in adjuvant systemic treatment, most women with a diagnosis of early ER-positive breast cancer now have good prognosis with 10-year survival >90%. Survivorship issues and the management of unfavourable treatment effects are of paramount importance. The adverse effects of endocrine therapy may have a marked negative impact on quality of life, treatment compliance, and on short- and long-term health consequences. Contemporary management involves multidisciplinary input from medical specialties (including oncologists, endocrinologists, breast surgeons, gynaecologists), allied health practitioners (physiotherapists, dieticians, exercise physiologists, psychologists) and general practitioners.

In randomized trials among postmenopausal women with early breast cancer, antiresorptive agents have not only demonstrated prevention of cancer treatment-induced bone loss but also reductions in the risk of disease recurrence and metastasis. An individual patient data meta-analysis<sup>7</sup> included 18 766 women with early breast cancer participating in 26 RCTs. Overall, 83% of all women received systemic chemotherapy, and 66% were node positive. Most studies included in this meta-analysis used zoledronic acid or clodronate. In the entire population, bisphosphonates reduced the risk of distant bone recurrence (RR = 0.83,  $P = .004$ ), with less certain effects on time to any breast cancer recurrence (RR = 0.94,  $P = .08$ ) or breast cancer mortality (RR = 0.91,  $P = .04$ ). In the postmenopausal subgroup ( $n = 11\,767$ ), bisphosphonates provided greater benefits, improving not only distant bone recurrence (RR = 0.72,  $P = .002$ ), but also any breast cancer recurrence (RR = 0.86,  $P = .002$ ) and breast cancer mortality (RR = 0.82,  $P = .002$ ). In the premenopausal subgroup, bisphosphonates had no significant effects on any of these outcomes. The absolute benefits in postmenopausal women were modest (10-year absolute benefit 2.2% for bone recurrence, 1.6% for nonbone recurrences, and 3.3% for breast cancer mortality).<sup>7</sup> While denosumab has demonstrated prevention of bone density loss and reductions in fracture rates,<sup>8</sup> data on long-term oncological outcomes including survival are yet to be reported. Therefore, current practice guidelines in the US and Europe<sup>9,10</sup> recommend that adjuvant zoledronic acid or clodronate should be considered in postmenopausal women to improve breast cancer outcomes, especially in patients deemed to be at high enough recurrence risk to receive adjuvant chemotherapy. For women considered at low risk of recurrence, such as a small, node-negative tumour, bisphosphonates may not provide a clinically meaningful oncologic benefit. The choice of bisphosphonate treatment regimen, if indicated may depend on patient preference, side effect profile, country-specific availability, and on costs and funding mechanisms by government or insurer. Especially where generic bisphosphonates are available, costs may be offset by savings on bone mineral density (BMD) assessments.

For women not receiving adjuvant bisphosphonates, the use of antiresorptive agents for prevention of bone loss will be the primary reason for their use.

### 3 | PURPOSE AND SCOPE

This position statement focuses on the optimal approaches to prevention and management of bone loss associated with endocrine therapy in ER-positive breast cancer, a common side effect of aromatase inhibitors and ovarian suppression. Accelerated bone loss can be further aggravated by the effects of chemotherapy, which is often given in addition to adjuvant endocrine therapy in high-risk patients with ER-positive breast cancer.

Specifically, we address the following key questions:

In women with early ER-positive breast cancer receiving adjuvant endocrine therapy,

- Does accelerated bone loss and increased fracture rates occur during endocrine therapy?
- What is the efficacy of nonpharmacological measures and pharmacotherapy in reducing the risk of adverse bone outcomes during endocrine therapy?
- How and when can fracture risk be assessed and monitored?
- When should pharmacotherapy with antiresorptive treatment be considered, which agent could be used, and how long can it be used?
- What is the risk of adverse effects with antiresorptive treatment?

This position statement is targeted towards health professionals involved in the clinical management of women with early breast cancer, including endocrinologists, oncologists, and general practitioners.

### 4 | METHODOLOGY

The Councils of the Endocrine Society of Australia (ESA), the Australian and New Zealand Bone & Mineral Society (ANZBMS), the Australasian Menopause Society (AMS), and the Clinical Oncology Society of Australia (COSA) invited expert representatives of the respective societies: ESA, MG; ANZBMS, FM; AMS, AV; COSA, EL; and additional authors with expertise in this field, to participate in a working group in 2017. A distinguished endocrinologist with experience leading national and international guidelines (HT) was appointed to advise the working group. A consumer representative (JH) was invited to participate and highlight priorities, and to write a perspective (see Appendix S1, found in the Supporting Information).

Regular communication within the working group was accomplished by email prior to and subsequent to a face-to-face meeting held in October 2017. All potential conflicts of interests of participating authors were declared prior to commencing drafting of the manuscript (Table S1). Position statement development used the process proposed by the ADAPTE working group<sup>11</sup> which includes;

(step 1) definition of the clinical questions; (step 2) search for source guidelines; (step 3) assess clinical content of source guidelines; (step 4) evaluation of the quality and coherence of source guidelines; (step 5) adaption of the recommendations; (step 6) external review of the adapted guideline and (step 7) adoption, endorsement and implementation of the adapted guideline. The members of the working group were tasked to develop questions to be answered and to identify, consider and cite relevant evidence. Evidence was obtained from existing international evidence-based guidelines, systematic reviews, relevant publications, supplemented by the multidisciplinary expertise of the expert working group. To identify and appraise contemporary evidence-based guidelines, we performed a systematic search of medical databases (PubMed, Cochrane Register and EMBASE) from 2012 to June 2017 with the assistance of a professional librarian. Assessment of previously published guidelines, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was conducted (S. Ramchand et al, manuscript in preparation).

All authors contributed to the writing of the manuscript and the final draft statement was agreed to by all authors. The draft statement was then submitted to the Councils of the ESA, ANZBMS, AMS and COSA who provided feedback. The working group responded to feedback and the final version was approved and submitted to Clinical Endocrinology in April 2018.

## 5 | EVIDENCE

### 5.1 | Does accelerated bone loss and increased fracture rates occur during endocrine therapy?

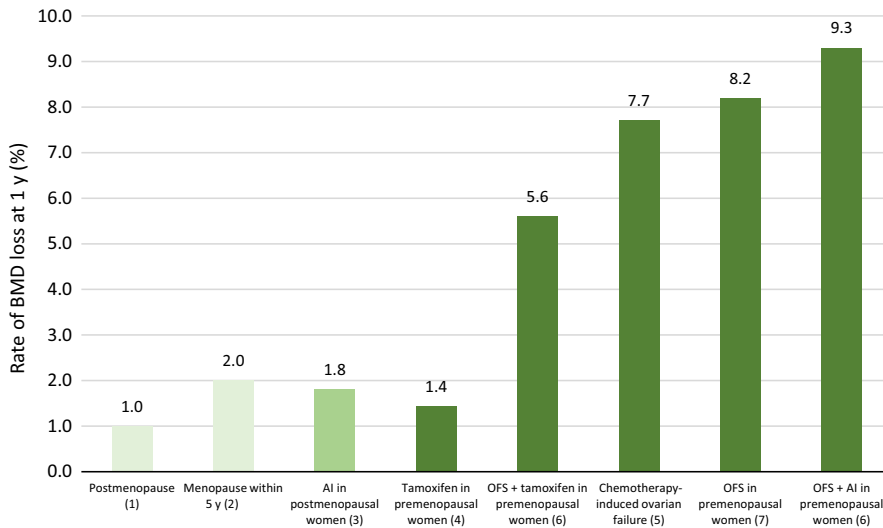
In postmenopausal women, aromatase inhibitors are associated with increased bone remodelling, a twofold to threefold acceleration in BMD decline, and increased fracture rates. In the bone substudy of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, hip BMD declined by 7.2% after 5 years of aromatase inhibitor treatment, and the magnitude of bone loss was greatest within the first 2 years.<sup>12</sup> In a meta-analysis of 7 RCTs enrolling 30 023 patients, aromatase inhibitor use was associated with a 47% increased fracture risk compared with tamoxifen (odds ratio 1.47; 95% CI 1.34-1.61;  $P < .001$ ).<sup>13</sup> The absolute difference between the 2 groups was 2.2%, with a number needed to harm (ie, to cause one fracture) of 46. Fracture rates were not uniformly collected and varied from 0.9% to 11.0% in these RCTs.<sup>13</sup> Fractures were not adjudicated as primary end-points and the true risk is likely underestimated; indeed, in a recent dedicated fracture end-point RCT, 10% of placebo-treated patients had a new clinical fracture within 3 years of aromatase inhibitor treatment.<sup>8</sup>

It is important to note that aromatase inhibitor-associated fracture rates reported in these studies may be confounded by the lack of placebo controls, and beneficial bone health effects of tamoxifen in postmenopausal women may confound interpretation of data on aromatase inhibitor use. Given the established benefit of tamoxifen on breast cancer outcomes, there is limited RCT evidence comparing the effects of aromatase inhibitor treatment on bone health with placebo. However, clinical data do support the notion that aromatase inhibitors

accelerate bone loss. In a bone substudy of a breast cancer prevention RCT in high-risk postmenopausal women without osteoporosis at baseline ( $T$ -score of at least  $-2.5$  at both spine and femoral neck) not receiving antiresorptive treatment, women randomized to anastrozole ( $n = 310$ ) had a significantly greater BMD decrease after 3 years of follow-up compared to women receiving placebo ( $n = 342$ ), both the at lumbar spine ( $-4.0\%$  [ $-4.5$  to  $-3.4$ ] vs  $-1.2\%$  [ $-1.7$  to  $-0.7$ ],  $P < .0001$ ) and at the total hip ( $-4.0\%$  [ $-4.4$  to  $-3.6$ ] vs  $-1.8\%$  [ $-2.1$  to  $-1.4$ ],  $P < .0001$ ).<sup>14</sup> In one RCT of 147 postmenopausal women with early breast cancer, 2-year aromatase inhibitor treatment, compared with placebo, increased bone loss at the femoral neck (2.72% vs 1.48%,  $P = .024$ ), but not at the lumbar spine, (2.17% vs 1.84%,  $P = .57$ ).<sup>15</sup> In an RCT of 1579 postmenopausal women randomized to aromatase inhibitor treatment vs placebo after 5-year treatment with tamoxifen, with a median follow-up of 5.3 years, self-reported new diagnoses of osteoporosis were increased and significantly more clinical fractures occurred in the women who received aromatase inhibitors (5.2% vs 3.1%,  $P = .02$ ).<sup>16</sup> In the aforementioned RCT of 1918 postmenopausal women with early breast cancer, 10 years of aromatase inhibitor treatment compared to 5 years of aromatase inhibitor treatment followed by 5 years of placebo led to a higher incidence of osteoporosis (10% vs 7%,  $P = .02$ ) and clinical fractures (133 vs 86,  $P = .001$ ), despite 50% of women in both groups receiving bisphosphonates during the study.<sup>6</sup> A recent meta-analysis combining RCTs and cohort studies estimated that aromatase inhibitor treatment increased fracture risk by 17% [95% CI 1.07-1.28] compared to no endocrine treatment.<sup>17</sup>

The largest magnitude of bone loss, 7%-9% at the lumbar spine in the first 12 months, occurs in premenopausal women with chemotherapy-induced menopause or concurrent ovarian suppression and aromatase inhibition (Figure 1, adapted from Gralow et al<sup>18</sup>). Alkylating chemotherapy and age  $>40$  years are associated with the highest risk of ovarian failure. In SOFT/TEXT, the use of ovarian suppression and aromatase inhibitor was associated with twice the prevalence of osteoporosis compared to ovarian suppression and tamoxifen use (13.2% vs 6.4% at 68 months).<sup>3</sup>

In contrast to its antagonistic actions on ER signalling in the breast, tamoxifen acts at a partial ER agonist at the bone. Therefore, tamoxifen has differential effects on BMD depending on ovarian oestradiol production, acting as an anti-oestrogen when endogenous concentrations of oestrogen are high but as an oestrogen when circulating oestrogen concentrations are low. In postmenopausal women with early breast cancer tamoxifen modestly increased BMD (+1.2% at the lumbar spine at 2 years vs  $-2.0\%$  with placebo).<sup>19</sup> In a 5-year RCT of more than 13 000 women at high risk of breast cancer, tamoxifen not only reduced the risk of invasive cancer but, after follow-up for an additional 7 years, reduced osteoporotic fracture risk by 32% (RR = 0.68, 95% CI = 0.51 to 0.92).<sup>20</sup> By contrast, in women who continue to menstruate after chemotherapy, tamoxifen (being less potent than native oestradiol) reduced lumbar spine BMD by 4.6% at 3 years of follow-up.<sup>21</sup> In a 2-year RCT of 89 premenopausal women with breast cancer receiving gonadotropin-releasing hormone (GnRH) agonist therapy, tamoxifen reduced goserelin-associated bone loss ( $-5\%$  with



**FIGURE 1** Annual rates of bone density loss at the lumbar spine (%). AI, aromatase inhibitor; OFS, ovarian function suppression with GnRH analogues. Adapted and updated from NCCN Taskforce Report: Bone Health in Cancer Care.<sup>18</sup> 1: Kanis et al,<sup>47</sup> 2: Finkelstein et al,<sup>48</sup> 3: Gnani et al,<sup>8</sup> 4: Powles et al,<sup>49</sup> 5: Shapiro et al,<sup>50</sup> 6: Gnani et al,<sup>30</sup> 7: Fogelman et al<sup>51</sup> [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

goserelin alone compared to -1.4% with goserelin and tamoxifen,  $P = .02$ .<sup>22</sup> In a study of 404 premenopausal women, 3-year lumbar spine BMD loss was 9.0% with goserelin plus tamoxifen compared to 13.6% with goserelin plus anastrozole.<sup>8</sup> Therefore, premenopausal women have increased bone loss during tamoxifen treatment, with the opposite observed in postmenopausal women.

## 5.2 | What is the efficacy of nonpharmacological measures and pharmacotherapy in reducing the risk of adverse bone outcomes during endocrine therapy?

The evidence regarding benefits of nonpharmacological measures specific to breast cancer survivors is limited. A recent systematic review and meta-analysis including 7 RCTs enrolling 1199 women with breast cancer in various exercise programs consisting of either progressive resistance training alone or in combination with impact loading exercises for at least 12 months did not demonstrate a benefit on bone density in postmenopausal women.<sup>23</sup> However, evidence from one large RCT ( $n = 498$ )<sup>24</sup> included in the meta-analysis<sup>23</sup> reported that exercise combining step aerobic and circuit-training reduced bone loss in premenopausal women at the femoral neck (mean BMD difference = 1.2%; 95% CI 0.2-2.2;  $P = .02$ ), but not at the lumbar spine. Moreover, accumulating evidence shows that exercise leads to multiple benefits in women with breast cancer, including improved quality of life, reduced aromatase inhibitor-associated arthralgia, and possible improved breast cancer outcomes.<sup>25,26</sup> Ongoing clinical trials are evaluating the effects of weight loss on oncological outcomes in obese women,<sup>27</sup> but effects on bone density and fracture are not known. Evidence regarding vitamin D and calcium supplementation specific to breast cancer survivors is not available.

In RCTs of postmenopausal women with early breast cancer, bisphosphonates consistently prevent endocrine therapy-induced bone loss. The data are strongest for zoledronic acid (Table 1). However, fracture outcome data for bisphosphonates are lacking. By contrast, the ABCSG-18 trial reported a 50% reduction in clinical fracture rates

with denosumab (60 mg given 6-monthly for 3 years) compared to placebo (HR 0.50; 95% CI 0.39-0.65;  $P < .0001$ ) in postmenopausal women receiving aromatase inhibitor treatment.<sup>8</sup> Although fracture numbers were small (overall  $n = 268$ ), the 55% of participants with normal baseline lumbar spine  $T$ -score ( $\geq -1.0$ ) had similar benefit from treatment with denosumab (HR 0.44; 95% CI 0.31-0.64;  $P < .0001$ ) compared to women with  $T$ -scores of  $< -1.0$  (HR 0.57; 95% CI 0.40-0.82;  $P < .0001$ ).<sup>8</sup> Placebo fracture incidence (clinical vertebral and nonvertebral) in this trial<sup>8</sup> was 162/10 000 person-years, comparable to placebo groups seen in recent placebo-controlled trials in established postmenopausal osteoporosis, 149/10 000 person-years in the HORIZON Recurrent Fracture Trial<sup>28</sup> and 209/10 000 person-years in the FREEDOM trial.<sup>29</sup> This was despite participants in the aromatase inhibitor study<sup>8</sup> being 5-10 years younger than the osteoporosis trial participants<sup>28,29</sup> and having bone density in the normal to osteopaenic ranges rather than osteoporosis.

In premenopausal women receiving concurrent aromatase inhibitor and ovarian suppression, marked bone loss was observed in women not receiving antiresorptive treatment (11% at the lumbar spine over 3 years) but this was completely prevented by 6-monthly administration of zoledronic acid.<sup>30</sup>

## 5.3 | How and when can fracture risk be assessed and monitored?

Clinical risk factors for osteoporosis and fragility fractures are common in women with breast cancer. Vitamin D insufficiency/deficiency has been reported in 64% of Australian,<sup>31</sup> and in 76% of American breast cancer survivors, with lower vitamin D levels observed in African American and Hispanic women.<sup>32</sup> Chemotherapy-induced neuropathy may increase falls risk. An Australian study<sup>31</sup> investigating causes of secondary osteoporosis in 200 women with breast cancer older than 50 years reported that 37% were current/previous smokers, 21% had elevated parathyroid hormone (PTH) levels (3% primary hyperparathyroidism), 5.5% had a history of hyperthyroidism, and 11.5% were taking oral/inhaled glucocorticoids.

**TABLE 1** Summary of major RCTs evaluating the efficacy of antiestrogenic therapies for aromatase inhibitor-induced bone loss (AIBL) in women with ER+ early breast cancer

Study	Population at study entry	Intervention	n	Dose, route of administration and duration of follow-up	Primary outcomes	Results
Parental therapies						
Safra et al (2011) <sup>53</sup>	Postmenopausal Median age 59 year, range 43-84 year T-score $\geq -2.5$ No prevalent fractures	Zoledronate Untreated Control	47 43	4 mg Q6M, IV 60 month	LS BMD up to 60 month	24 m (n = 57): Difference in 0.98 g/cm <sup>2</sup> and 0.63 g/cm <sup>2</sup> at spine and hip 48 m (n = 19): Difference in 0.87 g/cm <sup>2</sup> and 0.60 g/cm <sup>2</sup> at spine and hip Primary end-point at 60 m not evaluable (n = 15)
Gnant et al (2008) <sup>30</sup> ABCSC-12 Bone Substudy	Pre-menopausal, OFS + AI Median age 45 year, range 26-56 year T-score $\geq -2.5$ No prevalent fractures	Zoledronate Untreated Control	105 96	4 mg Q6M, IV 60 month (ET + ZOL/Placebo for 36 month and then stopped for 24 month)	BMD at 12 month	4 arm study: OS + Tam/AI and OS + Tam/AI + ZOL (total n = 414)—only AI results presented here 12 m: LS: +2.1% vs -5.6% in ZOL vs Control TH: no significant difference 36 m: LS +1.0% vs -9.0% in ZOL vs Control TH: +0.8% vs -7.3% in ZOL vs Control
Gnant et al (2015) <sup>8</sup> ABCSC-18	Postmenopausal >60 or BSO or <60 year + FSH and E2 in postmenopausal range Median age 64 year, range 38-91 year No T-score exclusion	Denosumab Placebo Control	1711 1709	60 mg Q6M, SC 36 month	Time to first clinical fracture	Time to first clinical fracture delayed in denosumab vs placebo HR 0.5 [95% CI 0.39-0.65], <i>P</i> < .0001 Fractures 92 vs 176 Fracture reduction irrespective of baseline BMD 36 m: LS: +7.27% vs -2.75% in denosumab vs placebo TH: +4.60% vs -3.32% in denosumab vs placebo
Ellis GK et al (2008) <sup>54,55</sup>	Postmenopausal Mean age 59 year, range 35-84 year T-score -1.0 to -2.5	Denosumab Placebo Control	127 125	60 mg Q6M, SC 24 month	BMD at 12 month	12 m: Difference in +5.5% at LS in denosumab vs placebo 24 m: Difference in +7.6% at LS, +4.7% at TH, +3.6% at FN in denosumab vs placebo

(Continues)

TABLE 1 (Continued)

Study	Population at study entry	Intervention	n	Dose, route of administration and duration of follow-up	Primary outcomes	Results
Oral therapies						
Greenspan et al (2015) <sup>56</sup>	Postmenopausal Mean age 65(R) and 64 (P) T-score -1.0 to -2.5 T-score < -2.5/prior FF allowed if treating team and patient agreeable after counselling about treatment options	Risedronate Placebo	55 54	35 mg QW, PO 24 month	LS and TH BMD at 24 month	12 m: LS: +2.0% vs -1.2% in risedronate (n = 50) vs placebo (n = 50) TH: +0.5% vs -1.6% in risedronate (n = 50) vs placebo (n = 50) 24 m: LS: +2.3% vs -1.7% in risedronate (n = 48) vs placebo (n = 47) TH: +0.6% vs -2.7% in risedronate (n = 48) vs placebo (n = 47)
Sestak et al (2014) <sup>14</sup> IBIS-II Bone Substudy	Postmenopausal or BSO Median age 60 year T-score -1.0 to -2.5	Risedronate Placebo Allowed to reduce frequency to fortnightly or drug holiday if severe adverse events	137 123	35 mg QW, PO 36 month	LS and TH BMD at 36 month	36 m: LS: +1.1% vs -2.6% in risedronate (n = 77) vs placebo (n = 73) TH: -0.7% vs -3.5% in risedronate (n = 77) vs placebo (n = 73)
Van Poznak et al (2010) <sup>57</sup> SABRE	Postmenopausal Mean age 64 year (R) and 65 year (P) T-score -1.0 to -2.0	Risedronate Placebo	77 77	35 mg QW, PO 24 month	LS BMD at 12 month	12 m: LS: +1.2% vs -1.2% in risedronate (n = 72) vs placebo (n = 62) TH: +0.9% vs -0.4% in risedronate (n = 72) vs placebo (n = 62) 24 m: LS: +2.2% vs -1.8% in risedronate (n = 60) vs placebo (n = 54) TH: +1.8% vs -1.1% in risedronate (n = 60) vs placebo (n = 54)
Markopoulos et al (2010) <sup>58</sup> ARBI	Postmenopausal Mean age 65 (R) and 63 year (P) T-score -1.0 to -2.5	Risedronate Placebo	37 33	35 mg QW, PO 24 month	LS and TH BMD at 12 month	12 m: LS and TH not significant (n = 57) 24 m: LS -5.7% vs -1.5% in risedronate (n = 26) vs placebo (n = 21) TH 1.6% vs 3.9% in risedronate (n = 26) vs placebo (n = 21)
Lester et al (2008) <sup>59</sup> ARIBON	Postmenopausal Median age 68 year T-score -1.0 to -2.5	Ibandronate Placebo	25 25	150 mg Q4W, PO 24 month	LS and TH BMD at 12 and 24 month	12 m: LS: +3.11% vs -2.35% in risedronate (n = 23) vs placebo (n = 25) TH: +0.98% vs -2.27% in risedronate (n = 23) vs placebo (n = 25) 24 m: LS: +2.98% vs -3.22% in risedronate (n = 21) vs placebo (n = 19) TH: +0.60% vs -3.90% in risedronate (n = 21) vs placebo (n = 19)

(Continues)

TABLE 1 (Continued)

Study	Population at study entry	Intervention	n	Dose, route of administration and duration of follow-up	Primary outcomes	Results
Immediate vs delayed therapy						
Bundred et al (2008) <sup>60</sup> ZO-FAST	Postmenopausal Median age 57 (I) and 58 (D), range 36-87 year T-score $\geq -2.0$ No prevalent fractures n = 1065 at baseline	Zoledronate— Immediate Zoledronate— Delayed <sup>a</sup>	533 532	4 mg Q6M, IV 12 month	LS BMD at 12 month	12 m: LS: +2.1% vs -3.5% in immediate (n = 467) vs delayed (n = 464) TH: Difference in +3.6% in immediate (n = 467) vs delayed (n = 464)
Eidtmann et al (2010) <sup>61</sup> ZO-FAST	Postmenopausal Median age 57 (I) and 58 (D), range 36-87 year T-score $\geq -2.0$ No prevalent fractures n = 1065 at baseline	Zoledronate— Immediate Zoledronate— Delayed <sup>b</sup>	533 532	4 mg Q6M, IV 36 month	LS BMD at 12 month	36 m: LS: +4.39% vs -4.9% in immediate (n = 314) vs delayed (n = 319) TH: Difference in +5.41% in immediate (n = 314) vs delayed (n = 319)
Coleman et al (2013) <sup>62</sup> ZO-FAST	Postmenopausal Median age 57 (I) and 58 (D), range 36-87 year T-score $\geq -2.0$ No prevalent fractures n = 1065 at baseline	Zoledronate— Immediate Zoledronate— Delayed <sup>b</sup>	533 532	4 mg Q6M, IV 60 month	LS BMD at 12 month	60 m: LS: +4.3% vs -5.7% in immediate (n = 264) vs delayed (n = 264) TH: +1.6% vs -4.2% in immediate (n = 264) vs delayed (n = 264)
Brufsky et al (2007) <sup>63</sup> Z-FAST	Postmenopausal Median age 60 year, range 35-89 year T-score $\geq -2.0$	Zoledronate— Immediate Zoledronate— Delayed <sup>a</sup>	301 301	4 mg Q6M, IV 12 month	LS BMD at 12 month	The least squares mean difference between groups in percentage change of BMD from baseline to month 12 for LS = 4.3% and total hip = 3.2% (Immediate n = 251, Delayed n = 256)
Brufsky et al (2009) <sup>64</sup> Z-FAST	Postmenopausal Median age 60 year, range 35-89 year T-score $\geq -2.0$	Zoledronate— Immediate Zoledronate— Delayed <sup>b</sup>	301 301	4 mg Q6M, IV 36 month	LS BMD at 12 month	The least squares mean difference between groups in percentage change of BMD from baseline to month 36 for LS = 6.7% and total hip = 5.3% (Immediate n = 189, Delayed n = 189)
Brufsky et al (2012) <sup>65</sup> Z-FAST	Postmenopausal Median age 60 year, range 35-89 year T-score $\geq -2.0$	Zoledronate— Immediate Zoledronate— Delayed <sup>b</sup>	301 301	4 mg Q6M, IV 61 month	LS BMD at 12 month	The least squares mean difference between groups in percentage change of BMD increased from baseline to month 61 for LS (4.3% to 8.9%) and total hip (3.2% to 6.7%)
Brufsky et al (2008) <sup>66</sup> Combined Z-FAST and ZO-FAST	Postmenopausal Median age 58(I) and 59(D), range 35-89 year T-score $\geq -2.0$	Zoledronate— Immediate Zoledronate— Delayed <sup>a</sup>	833 834	4 mg Q6M, IV 12 month	LS BMD at 12 month	The least squares mean difference between groups in percentage change of BMD from baseline to month 12 for LS = 5.2% and total hip = 3.5%

(Continues)



TABLE 1 (Continued)

Study	Population at study entry	Intervention	n	Dose, route of administration and duration of follow-up	Primary outcomes	Results
Lombart et al (2012) <sup>67</sup> E-ZO-FAST	Postmenopausal Median age 58, range 40-81 T-score $\geq$ -2.0 No prevalent fractures	Zoledronate— Immediate Zoledronate— Delayed <sup>b</sup>	252 270	4 mg Q6M, IV 12 month	LS BMD at 12 month	12 m: LS: +2.72 vs -2.71 in immediate vs delayed TH: +1.72 vs -1.59 in immediate vs delayed
	Postmenopausal starting aromatase inhibition after tamoxifen; >55 year with cessation of menses or <55 with 1-year cessation of menses or BSO Mean age 59 year T-score $\geq$ -2.0 No prevalent fractures	Zoledronate— Immediate Zoledronate— Delayed <sup>c</sup>	274 277	4 mg Q6M, IV 24 month	LS BMD at 12 month	12 m: LS: +3.66 vs -1.66% in immediate (n = 208) vs delayed (n = 221) TH: +1.02% vs -1.41% in immediate (n = 208) vs delayed (n = 221) FN: +2.08% vs -0.09% in immediate (n = 208) vs delayed (n = 221) 24 m: LS: +4.94% vs -2.28% in immediate (n = 179) vs delayed (n = 198) TH: +1.22% vs -3.34% in immediate (n = 179) vs delayed (n = 198) FN: +3.36% vs +0.54% in immediate (n = 179) vs delayed (n = 198)
Wagner-Johnston et al (2015) <sup>69</sup> NCCTG-NO3CC	Postmenopausal starting aromatase inhibition after tamoxifen; >55 year with cessation of menses or <55 with 1-year cessation of menses or BSO Mean age 59 year T-score $\geq$ -2.0 No prevalent fractures	Zoledronate— Immediate Zoledronate— Delayed <sup>c</sup>	274 277	4 mg Q6M, IV 60 month	LS BMD at 12 month	60 m: Difference in LS +9.42% in immediate (n = 118) vs delayed (n = 119) Significant differences at TH in immediate (n = 118) vs delayed (n = 119) (values not given)

BMD, bone mineral density; BSO, bilateral salpingo-oophorectomy; E2, oestradiol; ET, endocrine therapy; FN, femoral neck; FSH, follicle-stimulating hormone; IV, intravenous; LS, lumbar spine; M, months; OFS, ovarian function suppression (with goserelin); PO, oral; SC, subcutaneous; TS, T-score; TH, total hip; Q, every; W, week; ZOL, zoledronic acid.

<sup>a</sup>Delayed: ZOL started if fragility fracture or on study T-score < -2.0

<sup>b</sup>Delayed: ZOL started if fragility fracture or on study T-score < -2.0 or morphometric LS fracture detected at 36 mo.

<sup>c</sup>Delayed: ZOL started if fragility fracture or on study T-score < -2.0 or morphometric LS fracture detected at any point.

**TABLE 2** Summary of recommendations for evaluation of bone health in women with early breast cancer

Guideline	Baseline DXA	Frequency of subsequent scans	Details of fracture risk assessment	Assessment for morphometric fractures
Canadian guidelines <sup>70</sup>	Yes	No treatment with BMAs: every 5 y if low risk (FRAX 10 y < 10%) or 1-3 y if moderate risk (FRAX 10 y 10%-20%). Treated with BMAs: every 2 y or annually if osteopaenia	FRAX tool	No recommendation
EMAS position statement <sup>71</sup>	Yes	No details	Age >65 y, BMI <24 kg/m <sup>2</sup> , a personal history of fragility fracture >50 y, family history of hip fracture, glucocorticoid use >6 mo, prior/current history of smoking, alcohol consumption, Ca, PTH, 25OHD	No recommendation
ESMO guidelines <sup>72</sup>	Yes	1-2 y	FRAX tool, Ca, PO <sub>4</sub> , 25OHD, PTH, Cr Cl, SPEP	No recommendation
European Panel guidelines <sup>10</sup>	Yes	No recommendation	FRAX tool but only in post-menopausal women	No recommendation
Joint position statement of the IOF/CABS/ECTS/IEG/ESCEO/IMS/SIOG <sup>73</sup>	Yes	1-2 y	Smoking history, BMI <20 kg/m <sup>2</sup> , parental history of hip fracture, fragility fracture above age 50 y, oral glucocorticoid use >6 mo, 25OHD	No recommendation
Lithuanian guidelines <sup>74</sup>	Yes	As per Lithuanian Ministry of Health recommendations— not specified	Prior history of FF. If no FF +TS <-1.5 evaluate falls risk. If no FF + TS <-1.5 and >-2.5 + ≥1 falls risk factor detailed evaluation of fracture risk factors: age >65 y, low BMI <20 kg/m <sup>2</sup> , parental history of hip fracture, AI therapy >6 mo, tamoxifen in the premenopausal period, premature menopause (natural or medically induced), radiotherapy, oral glucocorticoids >7.5 mg per day over 3 mo, alcohol consumption, smoking	Yes. All patients at baseline
NCCN Task Force Report <sup>77</sup>	Yes	2 y; consider repeat scan in 1 y if bone loss risks have changed significantly or for a major therapeutic intervention	FRAX tool and annual height measurement	Vertebral fracture assessment (VFA) at time of DXA in everyone, if not available consider lateral T-L X-ray
Singapore Cancer Network Guidelines <sup>75</sup>	Yes	1-2 y	Personal history of FF as an adult, hip fracture in a first-degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, >2 standard drinks of alcohol daily, low body weight, lifelong low calcium intake, 25OHD, chronic illness (hyperthyroidism, hyperparathyroidism, inflammatory bowel disease)	No recommendation

25OHD, 25-hydroxy vitamin D; BL, baseline; BMAs, bone-modifying agents; Ca, serum calcium; Cr Cl, creatinine clearance; DXA, dual energy X-ray absorptiometry scan; FF, fragility fracture; PO<sub>4</sub>, phosphate; PTH, parathyroid hormone; SPEP, serum protein electrophoresis; TS, T-score (based on bone mineral density data).

Guidelines developed within the last 5 y were included.

## Women with early receptor positive breast cancer treated with aromatase inhibition +/- OFS

### Initial bone health evaluation in all women

History	Blood and Urine Tests	Imaging
Prior fragility fracture/s > 50 y Parental history of hip fracture Pre-existing metabolic bone conditions Age at menopause Smoking status Alcohol consumption >3 SD/day Assessment of falls risk Chronic glucocorticoid use $\geq$ 5 mg for $\geq$ 3 months Diabetes (type 1 or 2) Malabsorptive conditions Rheumatoid arthritis Low BMI <20 kg/m <sup>2</sup>	UEC, LFT, 25OHD, TSH, Ca, Mg, PO <sub>4</sub>  If reduced bone mass is present, also consider the following:  Serum PTH, coeliac serology  Serum and urine electrophoresis if age >60 y or presence of risk factors for myeloma  Urinary fractional calcium excretion rate (to assess for hypercalciuria)	1. Baseline BMD by DXA <i>Repeat 1 y after commencement of AI and then every 2 y or every 1 y if:</i> - annual bone loss > 5% at any site - T*-score <-1.5 at any site - Commencing/changing anti-resorptive therapy  2. Thoraco-lumbar x-ray or VFA by DXA <i>Baseline: postmenopausal women only or premenopausal women if Z-score &lt;-1.5. Subsequent analysis if T*-score &lt;-1.5, back pain or loss of height <math>\geq</math>4 cm</i>  <small>NB: VFA may miss vertebral fractures associated with mild height loss; thus, lateral radiographs would be preferential in individuals with a history of back pain or height loss.</small>

### Management

<p><b>Weight bearing exercise</b> <i>At least 30 min per day most days of the week</i></p> <p><b>Calcium</b> <i>1000-1200 mg daily</i> <i>Dietary sources<sup>#</sup> are optimal but if unable to achieve the recommended target through diet alone, consider supplemental elemental calcium</i></p> <p><b>25(OH)-Vitamin D</b> <i>Target level 75 nmol/L<sup>1</sup> (Do not exceed 150 nmol/L)</i></p>	<p><b>Anti-resorptive therapy</b></p> <p>We recommend anti-resorptive therapy if any of the following criteria are met:</p> <ul style="list-style-type: none"> <li>- Prevalent or incident fragility or morphometric fracture/s</li> <li>- T*-score &lt;-2.0 at any site</li> <li>- Annual bone loss <math>\geq</math>5% and/or <math>\geq</math>0.05 g/cm<sup>2</sup> considering baseline BMD and other fracture risk factors</li> <li>- FRAX 10-y risk for major fracture &gt;20% or hip fracture &gt;3% (for postmenopausal women only)**</li> </ul>
---	--

**FIGURE 2** Management algorithm. 25OHD, 25-hydroxy vitamin D; AI, aromatase inhibitor; Ca, calcium; LFT, liver function test; Mg, magnesium; PTH, parathyroid hormone; PO<sub>4</sub>, phosphate; TSH, thyroid-stimulating hormone; SD, standard drinks, OFS, ovarian function suppression (either bilateral oophorectomy or use of GnRH analogues; UEC, urea, electrolytes, creatinine; VFA, vertebral fracture analysis, BMI, body mass index. \*For women <50 y, Z-score should be used instead of T-score. \*\*FRAX tool not validated for women <40 y old. FRAX may also underestimate fracture risk in women being treated with AI as this is not included in the algorithm. <sup>#</sup>[https://osteoporosis.org.au/sites/default/files/files/Calcium Fact Sheet 2nd Edition.pdf](https://osteoporosis.org.au/sites/default/files/files/Calcium%20Fact%20Sheet%202nd%20Edition.pdf). The recommendations do not apply to women who are receiving adjuvant bisphosphonates to improve breast cancer outcomes, or to women with natural menopause receiving endocrine treatment with tamoxifen alone. <sup>1</sup>Holick et al<sup>52</sup>

As in the general population, age and PTH levels were significantly associated with lower BMD in this study.<sup>31</sup>

Clinical risk factors including age (>65 years), race (Caucasian), low body mass index (<20 kg/m<sup>2</sup>), history of osteoporosis or prior fragility fractures, parental history of hip fracture, menopausal status, oral glucocorticoid use, smoking and alcohol consumption should be ascertained in all women commencing endocrine therapy (Table 2, Figure 2). In addition, basic laboratory testing (including full blood examination, electrolytes and creatinine, calcium, phosphate,

alkaline phosphatase/liver function tests, thyroid-stimulating hormone, and 25-OH vitamin D) and dual energy X-ray absorptiometry (DXA) imaging are advised in all women. If reduced bone mass (T- or Z-scores < -1.0) is present, individualized assessment is needed to identify and exclude other causes of secondary osteoporosis (Figure 2). As in the general population, women considered to be high fracture risk, those with a history of  $\geq$ 4 cm of height loss or kyphosis and/or those with long-term glucocorticoid use should also be assessed for vertebral fractures. Lateral radiographs of the

**TABLE 3** Summary of recommendations for management of bone health in women with early breast cancer

Guideline	Weight-bearing exercise	Total daily calcium intake	Daily 25-OH vitamin D dose and target level	T-score to initiate antiresorptive therapy	Other recommendations for starting antiresorptive therapy	Recommended antiresorptive agents and dose
Canadian guidelines <sup>70</sup>	Yes	1200 mg	1000 IU daily; target level not specified	<-2.0 in postmenopausal women only	Postmenopausal FRAX 10 y 10%-20% of major fracture; Premenopausal or postmenopausal FRAX 10-y risk >20% of major fracture; Prevalent hip/spine FF or >1 FF	Zoledronate 4 mg q6mo, denosumab 60 mg q6mo, any oral bisphosphonate. No recommendations made favouring one agent over the other.
EMAS position statement <sup>71</sup>	Yes	1000 mg	800-1000 IU; target level not specified	≤-2.0	2 or more clinical risk factors for fracture (specific risk factors not specified—reference made to other guidelines); Women at intermediate or high risk of fracture	Bisphosphonates. Consider denosumab.
ESMO guidelines <sup>72</sup>	Yes, moderate intensity	1000 mg	1000-2000 IU; target level not specified	<-2.0	2 or more of the following risk factors: TS <-1.5, age >65, current/previous smoking history, BMI <20, parental history of hip fracture, fragility fracture above age 50 y, oral glucocorticoid use >6 mo; annual BMD loss ≥10% or ≥4%-5% if osteopaenic at baseline	Zoledronate 4 mg q6mo, denosumab 60 mg q6mo, any oral bisphosphonate. No recommendations made favouring one agent over the other.
European Panel guidelines <sup>10</sup>	Yes	1000 mg	1000-2000 IU; target level not specified	<-2.0	In postmenopausal women (natural/induced) if 2 or more clinical risk factors (risk factors not specified in guideline—reference made to other guidelines)	Premenopausal: Zoledronate 4 mg q6mo. Postmenopausal women: Zoledronate 4 mg q6mo, denosumab 60 mg q6mo, any oral bisphosphonate.
Joint position statement of the IOF/CABS/ECTS/IEG/ESCEO/IMS/SIOG <sup>73</sup>	Yes, moderate intensity	1200 mg for postmenopausal women	800-2000 IU; target level not specified	<-2.0	2 or more of the following risk factors: TS <-1.5, age >65, current/previous smoking history, BMI <20, parental history of hip fracture, fragility fracture above age 50 yo, oral glucocorticoid use >6 mo; Annual BMD loss ≥5%-10%	Denosumab 60 mg q6mo and zoledronate 4 mg q6mo are the preferred agents—denosumab when fracture risk is a concern and zoledronate when disease recurrence is the main priority
Lithuanian guidelines <sup>74</sup>	Yes	1000 mg	800-1000 IU; target level not specified	≤-2.5 and at least 1 fall risk factor	Osteoporotic fracture (clinical or morphometric) within the previous year; TS ≤-1.5 and >-2.5+ ≥2 RF for fracture + ≥1 fall RF	Denosumab 60 mg q6mo. Bisphosphonates not approved for cancer treatment-induced bone loss in Lithuania.
NCCN Task Force Report <sup>18</sup>	Yes, 30 min per day of moderate intensity	1200 mg	800-1000 IU; target level not specified	≤-2.0, consider if TS between -1.5 and -2.0	FRAX 10-y fracture risk >20% for major fracture and >3% for hip fracture	No recommendations made favouring one agent over the other (oral BP or zoledronate or denosumab). Consider parental therapy in patients who are nonadherent to oral therapy.
Singapore Cancer Network Guidelines <sup>75</sup>	Yes	1200-1500 mg	800 IU; target level not specified	<-2.0	Consider if TS between -1.5 and -2.0 and 2 additional clinical risk factors for fracture (advanced age, FF as an adult, hip fracture in a first-degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, >2 standard units of alcohol daily, low body weight, lifelong low calcium intake, vitamin D deficiency, chronic illness (hyperthyroidism, hyperparathyroidism, inflammatory bowel disease)	No recommendations made favouring one agent over the other (oral BP or zoledronate). Denosumab not covered by this guideline.

FF, fragility fracture; TS, T-score (based on bone mineral density data).

thoracolumbar spine can be used to assess for vertebral fractures (Figure 2). Vertebral fracture assessment (VFA) on DXA imaging may also be used for fracture screening; however, VFA may miss vertebral fractures associated with mild height loss; thus, lateral radiographs would be preferential in individuals with a history of back pain or height loss.

In women with early breast cancer, there is insufficient evidence regarding the clinical usefulness of measuring bone remodelling markers in predicting fracture risk and monitoring treatment effects of antiresorptive agents. Routine monitoring of markers of bone remodelling (serum C-telopeptide [CTX]) and bone formation (N-terminal propeptide of type 1 procollagen [P1NP]) is not recommended. The utility of bone imaging other than DXA, such as high resolution peripheral quantitative computed tomography<sup>33</sup> also requires further evaluation.

The World Health Organization Fracture Risk Assessment Tool (FRAX) does not take aromatase inhibitor treatment or chemotherapy into consideration and is not validated for use in women <40 years. Therefore, FRAX may substantially underestimate fracture risk in women receiving these treatments.

DXA should be repeated 12 months after commencement of endocrine therapy, with subsequent individualized monitoring frequency (Table 2, Figure 2).

#### 5.4 | When should pharmacotherapy with antiresorptive treatment be considered, which agent could be used, and how long can these it be used?

Despite the lack of rigorous evidence specific to breast cancer survivors, general measures to prevent bone loss are recommended for all women starting endocrine therapy including ensuring calcium and vitamin D sufficiency (Figure 2). Exercise, including impact and resistance training, has multiple benefits for women with breast cancer in addition to bone health,<sup>25,34</sup> and weight-bearing exercise is recommended in all guidelines (Table 3). All women with breast cancer are advised to stop smoking and minimize alcohol consumption. Where possible, medications with adverse effects on BMD should be avoided.

In line with recommendations of the National Osteoporosis Foundation for the general population,<sup>35</sup> women with a fragility fracture (including subclinical vertebral fracture) or women  $\geq 70$  years with a BMD *T*-score  $\leq -2.5$  could commence antiresorptive therapy unless contraindicated. There is limited evidence specific to women receiving endocrine therapy to guide recommendations outside these criteria. Although recommendations differ slightly between guidelines (Table 3), antiresorptive therapy can be considered in aromatase inhibitor-treated women not fulfilling the National Osteoporosis Foundation criteria if the BMD *T*-score is  $< -2.0$  at any site,  $\geq 2$  fracture risk factors are present, there is a  $\geq 5\%$  and/or  $\geq 0.05$  g/cm<sup>2</sup> decrease in BMD in 1 year, considering baseline BMD and other fracture risk factors, or if the FRAX 10-year risk for major fracture is  $>20\%$  or hip fracture is  $>3\%$  (Figure 2). Other commentators have suggested that antiresorptive treatment may be warranted

in women with *T*-scores between  $-1.5$  and  $-2.0$ , if 2 or more clinical risk factors for fracture are present.<sup>36</sup> Notably, governmental subsidy for the use of antiresorptive therapy in these circumstances varies in different countries.

In premenopausal women, accelerated bone loss with cancer therapies occurs predominantly through treatment-induced suppression/failure of ovarian function and through the inhibition of oestrogen effect on bone. In women who receive GnRH analogues for ovarian suppression or experience ovarian failure, some recovery of bone density occurs in those who subsequently resume menses. In women receiving concurrent aromatase inhibitors and GnRH analogues, bone loss is most pronounced (Figure 1). Current guidance from expert groups for premenopausal women recommends that all premenopausal women be informed about the potential for bone loss during anticancer therapy. Premenopausal women commonly have normal baseline BMD with low short-term fracture risk yet lose bone more rapidly than older postmenopausal women. Decisions regarding antiresorptive treatment should be carefully discussed with each woman. In premenopausal women, if the *Z*-score is  $< -2.0$ , or if the *Z*-score is  $< -1.0$  and there has been an annual decrease in BMD of 5%, antiresorptive therapy may be considered.<sup>37</sup> Zoledronic acid is the only bisphosphonate which has been shown to prevent bone loss associated with concurrent ovarian suppression and tamoxifen/anastrozole therapy<sup>38</sup> or with chemotherapy-induced ovarian failure,<sup>39</sup> and data regarding denosumab are lacking in this setting. There is a lack of long-term follow-up of premenopausal women who experience bone loss during breast cancer therapy to guide fracture risk assessment. The uncertainties regarding optimal fracture risk assessment and management in premenopausal women treated for breast cancer is an area deserving of further research.

The duration of antiresorptive treatment should be individualized based on absolute fracture risk. In most untreated women, bone loss is most marked in the 12-24 months postaromatase inhibitor initiation, and limited data suggest partial BMD recovery after cessation of endocrine therapy. Most guidelines (Table 3) comment on the uncertainty regarding the duration of antiresorptive treatment during endocrine therapy. In women with the highest baseline risk of fracture, antiresorptive treatment may need to be continued until the adjuvant breast cancer treatment is complete or even longer.

Zoledronic acid trials in this population have used 4 mg every 6 months (Table 1). Alternative dosing schedules using 5 mg every 12 months, with antifracture efficacy in other populations<sup>40</sup> may be relevant here but are yet to be trialled in this population.

The bisphosphonates alendronate and zoledronic acid persist in the bone matrix for years after therapy is discontinued. In contrast, there may be an increased risk of multiple vertebral fractures soon after discontinuation of denosumab, particularly among those with pre-existing vertebral fractures,<sup>41</sup> including case reports of women treated with aromatase inhibitors.<sup>42</sup> Preclinical evidence suggests that accelerated bone remodelling may promote the development of skeletal metastasis.<sup>43</sup> Denosumab should be given strictly 6-monthly, and a delay in dosing should be avoided. Based on currently available data, it is recommended that denosumab

should not be stopped without considering alternative treatment with a bisphosphonate to decrease the rebound BMD loss and vertebral fracture risk. The optimal timing of initiation and mode and duration of bisphosphonate administration following cessation of denosumab is unclear.

Currently, the use of antiresorptive treatment in this population is generally off-label. However, off-label use is supported by evidence in this and the general population and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

### 5.5 | What is the risk of adverse effects with antiresorptive agents?

Antiresorptive therapies are generally well tolerated, especially if dosing regimens used in osteoporosis studies are prescribed. However, discussion with the individual woman regarding potential side effects is necessary. Zoledronic acid is associated with an acute-phase reaction (typically within 24-72 hours of the first infusion), and treatment with antipyretic agents generally improves these symptoms. In addition, all bisphosphonates carry a warning regarding use in patients with severe renal impairment (creatinine clearance <35 mL/min). Severe hypocalcaemia has been observed in patients with chronic kidney disease stage 4-5, treated with denosumab despite 25-hydroxyvitamin D sufficiency, with recommendations for caution in this group.<sup>44</sup>

Osteonecrosis of the jaw is a potential complication of bisphosphonate and denosumab therapy. Osteonecrosis of the jaw is rare (estimated risk 1:10 000 to 1:100 000) when antiresorptives are prescribed in doses approved for osteoporosis treatment.<sup>10</sup>

Another concern arising from longer term antiresorptive use is atypical femoral fracture. Atypical femoral fractures are more common in patients exposed to long-term bisphosphonates, with higher risk (113 per 100 000 person-years) in patients who receive more than 7-8 years of therapy.<sup>45</sup> Therefore, especially in women with extended aromatase inhibitor treatment who have received antiresorptive treatment for 5 years or longer, have had no fragility fractures, and have maintained stable bone density in the osteopaenic range, consideration of treatment cessation and a period of monitoring should be given (see considerations for denosumab above). Of note, the risk of a subsequent atypical femoral fracture is reduced following 12 months of bisphosphonate cessation.<sup>45</sup>

In women who desire future pregnancy, the risks and benefits of antiresorptive therapy should be assessed on an individual basis, particularly in those in whom resumption of menses occurs following breast cancer treatment cessation. Long-acting bisphosphonates accumulate and persist in the maternal skeleton for years, even following drug cessation. Limited data suggest that maternal use of bisphosphonates during or prior to pregnancy does not have serious foetal or neonatal adverse effects.<sup>46</sup> However, bisphosphonates should ideally be ceased at least 1 year prior to pregnancy.

## 6 | CONCLUSIONS

Prior to commencement of adjuvant endocrine therapy, all women should be counselled about associated side effects. Adverse effects on skeletal health should be considered in the decision-making process especially in women at high risk for fractures. Treating clinicians should be assiduous in ascertaining treatment-related adverse effects and pursue interventions known to mitigate these effects and enhance treatment adherence. Management is best individualized, using a multidisciplinary approach. Key priorities for future research include the conduct of future clinical trials to delineate better the long-term fracture risks of adjuvant endocrine therapy and to determine the efficacy of interventions designed to mitigate these risks. Availability of robust data on fracture rates and their prevention are also important to generate health economic data to inform health policy.

### ACKNOWLEDGEMENTS

The authors would like to thank the ESA Council (chair Associate Professor Warrick Inder), the ANZBMS Council (chair Professor Emma Duncan during the writing and reviewing of this report), the ANZBMS Therapeutics Committee (chair Professor Richard Prince), the ANZBMS Densitometry Committee (chair Associate Professor Nicholas Pocock), the AMS board members, the AMS Executive Director and AMS Past Presidents Doctors Jane Elliott and Anna Fenton, and the COSA council (chair Professor Phyllis Butow) for their support, expert reviews and valuable contributions to this manuscript.

### DISCLOSURE SUMMARY

See Table S1 (found in the Supporting Information)

### ORCID

Mathis Grossmann  <http://orcid.org/0000-0001-8261-3457>

Helena Teede  <http://orcid.org/0000-0001-7609-577X>

### REFERENCES

- Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* 2005;97:1262-1271.
- Early Breast Cancer Trialists' Collaborative Group, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386:1341-1352.
- Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2014;371:107-118.
- Saha P, Regan MM, Pagani O, et al. Treatment efficacy, adherence, and quality of life among women younger than 35 years in the

- International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials. *J Clin Oncol*. 2017;35:3113-3122.
5. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381:805-816.
  6. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med*. 2016;375:209-219.
  7. Early Breast Cancer Trialists' Collaborative Group, Coleman R, Powles T, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. 2015;386:1353-1361.
  8. Gnant M, Pfeiler G, Dubsy PC, et al. Adjuvant denosumab in breast cancer (ABCSC-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;386:433-443.
  9. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2017;35:2062-2081.
  10. Hadji P, Coleman RE, Wilson C, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Ann Oncol*. 2016;27:379-390.
  11. Fervers B, Burgers JS, Haugh MC, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. *Int J Qual Health Care*. 2006;18:167-176.
  12. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol*. 2008;26:1051-1057.
  13. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103:1299-1309.
  14. Sestak I, Singh S, Cuzick J, et al. Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial. *Lancet Oncol*. 2014;15:1460-1468.
  15. Lonning PE, Geisler J, Krag LE, et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol*. 2005;23:5126-5137.
  16. Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol*. 2008;26:1948-1955.
  17. Tseng OL, Spinelli JJ, Gotay CC, Ho WY, McBride ML, Dawes MG. Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. *Ther Adv Musculoskelet Dis*. 2018;10:71-90.
  18. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: bone health in cancer care. *J Natl Compr Canc Netw*. 2013;11(Suppl. 3):S1-S50; quiz S51.
  19. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med*. 1992;326:852-856.
  20. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 2005;97:1652-1662.
  21. Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. *J Clin Oncol*. 2006;24:675-680.
  22. Sverrisdottir A, Fornander T, Jacobsson H, von Schoultz E, Rutqvist LE. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. *J Clin Oncol*. 2004;22:3694-3699.
  23. Fornusek CP, Kilbreath SL. Exercise for improving bone health in women treated for stages I-III breast cancer: a systematic review and meta-analyses. *J Cancer Surviv*. 2017;11:525-541.
  24. Saarto T, Sievanen H, Kellokumpu-Lehtinen P, et al. Effect of supervised and home exercise training on bone mineral density among breast cancer patients. A 12-month randomised controlled trial. *Osteoporos Int*. 2012;23:1601-1612.
  25. Casla S, Lopez-Tarruella S, Jerez Y, et al. Supervised physical exercise improves VO2max, quality of life, and health in early stage breast cancer patients: a randomized controlled trial. *Breast Cancer Res Treat*. 2015;153:371-382.
  26. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol*. 2012;30:3697-3704.
  27. Ligibel JA, Barry WT, Alfano C, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. *NPJ Breast Cancer*. 2017;3:37.
  28. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007;357:1799-1809.
  29. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.
  30. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSC-12 bone-mineral density substudy. *Lancet Oncol*. 2008;9:840-849.
  31. Mann GB, Kang YC, Brand C, Ebeling PR, Miller JA. Secondary causes of low bone mass in patients with breast cancer: a need for greater vigilance. *J Clin Oncol*. 2009;27:3605-3610.
  32. Neuhouser ML, Sorensen B, Hollis BW, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. *Am J Clin Nutr*. 2008;88:133-139.
  33. Ramchand SK, Seeman E, Wang XF, et al. Premenopausal women with early breast cancer treated with estradiol suppression have severely deteriorated bone microstructure. *Bone*. 2017;103:131-135.
  34. Winters-Stone KM, Dobek J, Nail LM, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteoporos Int*. 2013;24:1637-1646.
  35. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25:2359-2381.
  36. Santen RJ. Clinical review: effect of endocrine therapies on bone in breast cancer patients. *J Clin Endocrinol Metab*. 2011;96:308-319.
  37. Hadji P, Gnant M, Body JJ, et al. Cancer treatment-induced bone loss in premenopausal women: a need for therapeutic intervention? *Cancer Treat Rev*. 2012;38:798-806.
  38. Gnant M, Mlineritsch B, Stoeger H, et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozole 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;26:313-320.
  39. Shapiro CL, Halabi S, Hars V, et al. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. *Eur J Cancer*. 2011;47:683-689.
  40. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356:1809-1822.

41. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Miner Res.* 2018;33:190-198.
42. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after Denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res.* 2017;32:1291-1296.
43. Croucher PI, McDonald MM, Martin TJ. Bone metastasis: the importance of the neighbourhood. *Nat Rev Cancer.* 2016;16:373-386.
44. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. *Am J Nephrol.* 2015;41:129-137.
45. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2016;31:1910.
46. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. *Am J Health Syst Pharm.* 2014;71:2029-2036.
47. Kanis JA. Pathogenesis of osteoporosis and fracture. In: Ja K, ed. *Osteoporosis.* London, UK: Blackwell Healthcare Communications; 1997:22-55.
48. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab.* 2008;93:861-868.
49. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol.* 1996;14:78-84.
50. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol.* 2001;19:3306-3311.
51. Fogelman I, Blake GM, Blamey R, et al. Bone mineral density in premenopausal women treated for node-positive early breast cancer with 2 years of goserelin or 6 months of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). *Osteoporos Int.* 2003;14:1001-1006.
52. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:1911-1930.
53. Safra T, Bernstein-Molho R, Greenberg J, et al. The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: a prospective, randomized, phase II trial. *Oncology.* 2011;81:298-305.
54. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non-metastatic breast cancer. *J Clin Oncol.* 2008;26:4875-4882.
55. Ellis GK, Bone HG, Chlebowski R, et al. Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. *Breast Cancer Res Treat.* 2009;118:81-87.
56. Greenspan SL, Vujevich KT, Brufsky A, et al. Prevention of bone loss with risenedronate in breast cancer survivors: a randomized, controlled clinical trial. *Osteoporos Int.* 2015;26:1857-1864.
57. Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor-induced bone loss using risenedronate: the SABRE trial. *J Clin Oncol.* 2010;28:967-975.
58. Markopoulos C, Tzoracoleftherakis E, Polychronis A, et al. Management of anastrozole-induced bone loss in breast cancer patients with oral risenedronate: results from the ARBI prospective clinical trial. *Breast Cancer Res.* 2010;12:R24.
59. Lester JE, Dodwell D, Purohit OP, et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clin Cancer Res.* 2008;14:6336-6342.
60. Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer.* 2008;112:1001-1010.
61. Eidtmann H, de Boer R, Bundred N, et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Ann Oncol.* 2010;21:2188-2194.
62. 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;24:398-405.
63. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol.* 2007;25:829-836.
64. Brufsky AM, Bosserman LD, Caradonna RR, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. *Clin Breast Cancer.* 2009;9:77-85.
65. Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer.* 2012;118:1192-1201.
66. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist.* 2008;13:503-514.
67. Llombart A, Frassoldati A, Pajja 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;12:40-48.
68. Hines SL, Mincey B, Dentchev T, et al. Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. *Breast Cancer Res Treat.* 2009;117:603-609.
69. Wagner-Johnston ND, Sloan JA, Liu H, et al. 5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (Alliance) trial. *Cancer.* 2015;121:2537-2543.
70. Paterson AH, Shea-Budgell MA. Bone health in patients with breast cancer: recommendations from an evidence-based Canadian Guideline. *J Clin Med.* 2013;2:283-301.
71. Tremollieres FA, Ceausu I, Depypere H, et al. Osteoporosis management in patients with breast cancer: EMAS position statement. *Maturitas.* 2017;95:65-71.
72. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J, ESMO Guidelines Working Group. Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2014;25(suppl 3):iii124-137.
73. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol.* 2017;7:1-12.
74. Juozaityte E, Aleknavicius E, Janciauskiene R, et al. Guidelines for diagnostics and treatment of aromatase inhibitor-induced bone loss in women with breast cancer: a consensus of Lithuanian medical



oncologists, radiation oncologists, endocrinologists, and family medicine physicians. *Medicina (Kaunas)*. 2014;50:197-203.

75. Singapore Cancer Network Breast Cancer Workgroup. Singapore Cancer Network (SCAN) guidelines for bisphosphonate use in the adjuvant breast cancer setting. *Ann Acad Med Singapore*. 2015;44:368-378.

#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Grossmann M, Ramchand S, Milat F, et al. Assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy: Position statement of the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia. *Clin Endocrinol (Oxf)*. 2018;89:280-296. <https://doi.org/10.1111/cen.13735>