

Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

The Singapore Cancer Network (SCAN) Breast Cancer Workgroup

Abstract

Introduction: The SCAN breast cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines regarding the optimal time-point for initiation of bisphosphonates when using adjuvant aromatase inhibitors (AIs) and provide a consensus for their role in modifying clinical breast cancer outcomes. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Six international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2015), the European Society of Medical Oncology (2014), the National Institute for Clinical Evidence (2012), the Scottish Intercollegiate Guidelines Network (2013), the British Columbia Cancer Agency (2013) and the treatment algorithm based on the National Osteoporosis Foundation guidelines (2006). Recommendations on the use of bisphosphonates in postmenopausal women initiating adjuvant AIs in breast cancer to preserve bone health and the use of adjuvant bisphosphonates to improve breast cancer outcomes were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines on the use of adjuvant bisphosphonates to influence breast cancer outcomes and maintenance of bone health when on AIs.

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Key words: Aromatase inhibitors, Bone health, Breast cancer outcomes

Introduction

Breast cancer is the leading female cancer in our multiethnic Singaporean population and the most frequent cause of cancer mortality in females. The age-standardised incidence rate of newly diagnosed breast cancers in females has increased almost 3-fold in the last 4 decades from 23.8 per 100,000 in 1975 to 1979 to 64.7 per 100,000 in 2010 to 2014.¹ With our rapidly aging population demographics, the percentage of total breast cancers in women aged 55 years and above has correspondingly increased from 43.4% in 2004 to 2008 to 51.3% in 2009 to 2013.¹ Fortunately, due to improved education, increased public awareness and the implementation of our national screening programme, the majority of breast cancers are now being diagnosed earlier. Hormone receptor-positive breast cancers comprise the most common breast cancer subtypes, accounting for 75% of the cases.

The selective estrogen receptor modulator, tamoxifen, has been the standard of care in the adjuvant hormone-receptor positive setting for close to 3 decades, but

over the past 10 years, the advent of third-generation aromatase inhibitors (AIs) such as anastrozole, letrozole and exemestane has improved clinical outcomes in terms of breast cancer recurrence for postmenopausal women. The utility of AIs with respect to disease-free survival (DFS) has been demonstrated when administered as upfront therapy as shown in the Arimidex or Tamoxifen Alone or in Combination (ATAC) and Breast International Group (BIG) 1-98 studies,^{2,3} sequentially after 2 to 3 years of tamoxifen as in the International Exemestane Study (IES), the Italian Tamoxifen Anastrozole (ITA) and Arimidex-Nolvadex (ARNO) 95/Austrian Breast and Colorectal Study Group (ABCSG) 8 trials⁴⁻⁶ or after 5 years of tamoxifen as in the MA.17 data.⁷

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2015 meta-analyses comparing a 5-year course of an AI versus tamoxifen, a 5-year course of an AI versus 2 to 3 years of tamoxifen, then an AI to year 5, and 2 to 3 years of tamoxifen followed by an AI to year 5 versus 5 years of tamoxifen demonstrated that AIs gave a 30%

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proportionate reduction in recurrence rates compared with tamoxifen while treatments differed but not thereafter. Additionally, 5 years of an AI reduced the 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen.⁸

However, a common side effect of AIs is bone loss resulting in increased risk of osteoporotic fractures, due to their action of inhibiting the conversion of peripheral androgens to estrogen and causing a decline in estrogen levels. This is an especially pertinent issue in Singapore as since the 1960s, osteoporotic hip fractures have increased 5-fold in women over the age of 50, the age group in which AIs will potentially be used.

Bisphosphonates, although introduced as bone protective agents in osteoporosis management, now form an integral part of the treatment armamentarium to reduce cancer therapy-induced bone loss in breast cancer patients. Bisphosphonates are specific inhibitors of osteoclast-mediated bone resorption consisting of 2 major groups: non-nitrogen containing (clodronate and etidronate) and nitrogen containing or aminobisphosphonates (alendronate, risedronate, pamidronate and zoledronate).⁹ While oral bisphosphonates are generally well tolerated by most women, some have upper gastrointestinal tract adverse effects such as nausea (~4% to 11%), vomiting (≤1% to 3%), abdominal pain (~1% to 12%) and dyspepsia (~1% to 11%).¹⁰⁻¹³ There are some less common but potentially serious side effects of intravenous bisphosphonates including hypocalcaemia (≤3% to 17%), renal toxicity (~8% to 20%) and osteonecrosis of the jaw [ONJ] (~1% to 2%).^{10,14,15} Because of the risk of ONJ especially with intravenous bisphosphonates, and the attendant debilitating consequences, early screening and initiation of appropriate dental care are recommended before commencing bisphosphonate therapy.¹⁶ Patients should inform the dentist of their use of bisphosphonates before undergoing dental procedures.

In addition to bone protective effects, preclinical models have revealed an antitumour effect of bisphosphonates,^{17,18} leading to several clinical trials investigating their adjuvant use to improve cancer outcome in early breast cancer. Some data including a meta-analysis showed promising clinical outcomes¹⁹⁻²¹ while benefit was not demonstrated in some other studies.²² The exact mechanism for a possible antitumour effect of bisphosphonates remains unclear. In light of the complexity of this issue, guidelines are needed to aid the decision-making process with regard to using bisphosphonates to influence breast cancer outcomes.

The SCAN Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

The SCAN Guidelines are clinical practice guidelines for bisphosphonate use in early breast cancer patients.

This includes 1) women who may need bisphosphonates to preserve bone health when initiating AI therapy, or 2) women with primary breast cancer who may be considered for bisphosphonates as adjuvant therapy to improve breast cancer outcomes irrespective of their bone health.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for these management issues. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with breast cancer.

Guideline Recommendations/Development

The SCAN breast cancer workgroup comprises a panel of 11 medical oncologists and 1 oncology pharmacist from Singapore with special subspecialty interest in the management of breast cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework²³ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, specific breast cancer-related issues of relevance were identified and the scope and distribution of tasks was finalised. High quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The guidelines were chosen based on their high quality, currency and applicability to

our patient population. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 2 main management issues which were selected for this topic:

1. Use of bisphosphonates to preserve bone health in postmenopausal women initiating adjuvant AIs in breast cancer.
2. Use of adjuvant bisphosphonates to improve breast cancer outcomes.

For the first management issue, 5 international guidelines were selected for review (Supplementary Table 1):

- “NCCN Guidelines for Breast Cancer Version 3.2015” (v3.2015) by the National Cancer Comprehensive Network (NCCN, USA)²⁴
- “Bone Health in Cancer Patients: ESMO Clinical Practice Guidelines”, April 2014²⁵
- “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment” by the National Institute for Clinical Evidence (NICE), February 2009²⁶ Last reviewed on April 2012 and decision made not to update pre-existing guidelines at that time.
- “SIGN 134. Treatment of Primary Breast Cancer” by the Scottish Intercollegiate Guidelines Network (SIGN); September 2013²⁷
- “Aromatase Inhibitors and Bone Health in Women with Breast Cancer”—Treatment Algorithm Based on the National Osteoporosis Foundation Guidelines²⁸

For the second management issue, guideline availability was limited. The following 2 guidelines were considered (Supplementary Table 2):

- “Bone Health in Cancer Patients: ESMO Clinical Practice Guidelines”, April 2014²⁵
- “Breast Cancer Management. Bone Modifying Agents” by the British Columbia (BC) Cancer Agency, January 2013²⁹

Although the following 3 guidelines were screened, 1) and 2) were considered of limited utility as they were released more than 10 years ago (2003, 2004), and 3) did not have a formal recommendation:

1. “Update on the Role of Bisphosphonates and Bone Health Issues in Women with Breast Cancer” by the American Society of Clinical Oncology, 2003³⁰
2. “Use of Bisphosphonates in Women with Breast Cancer” by the Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC) and Cancer Care Ontario (CCO), April 2004.³¹ Reviewed in February 2012 and update in progress.
3. “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment” by NICE, February 2009²⁶

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of breast cancer with regard to bisphosphonate use, it will be reviewed earlier.

1. Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant AIs in Breast Cancer

Oral Bisphosphonates

The use of bisphosphonates to reduce therapy-induced bone loss has been investigated in several clinical studies. Earlier studies have evaluated oral bisphosphonates such as clodronate³² and risedronate^{33,34} with 2-year mean differences in lumbar spine (LS) bone mineral density (BMD) ranging from +2.2% to 2.9%, and hip BMD of up to +3.7% in favour of bisphosphonate-containing over no bisphosphonate or placebo arms. The ARIBON trial of oral ibandronate (150 mg/month) versus placebo for 2 years in postmenopausal women with hormone receptor-positive early breast cancer having osteopenia while on anastrozole showed a significant increase in LS and hip BMD of 2.98% and 0.6% respectively in the ibandronate group compared to placebo ($P < 0.01$), with no fragility fractures in either group.³⁵

Intravenous Zoledronate

More recent trials have focused on the efficacy of intravenous zoledronate. In particular, the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 bone substudy which randomised premenopausal women with hormone receptor (HR)-positive early breast cancer to receive endocrine therapy (goserelin/anastrozole or goserelin/tamoxifen) alone or with adjuvant zoledronate (4 mg, 6-monthly) for 3 years reported increased LS (+4%, $P = 0.02$) and trochanter (+3.9%, $P = 0.07$) BMD from baseline at 5 years.³⁶ For those not receiving zoledronate, the LS and trochanter BMD remained below baseline even at 5 years. The study was not powered to assess proportion of fractures between groups.

The Z-FAST and ZO-FAST trials studied the efficacy

of zoledronate (4 mg, 6-monthly) given up to a maximum of 5 years, either upfront or in a delayed fashion based on BMD T-scores <-2.0 or non-traumatic fractures, in postmenopausal women receiving adjuvant letrozole. In the Z-FAST study, the mean differences in LS and total hip BMD between upfront versus delayed therapy at 5 years were +8.9% and +6.7% respectively ($P < 0.0001$ for both) in favour of upfront zoledronate, with no significant difference in fracture rates.³⁷ Mean differences at 5 years in LS and total hip BMD between the upfront and delayed groups were +4.3% and -5.4% ($P < 0.0001$) in the ZO-FAST trial, with statistically similar fracture rates in both groups.³⁸

Treatment Algorithm Based on the National Osteoporosis Foundation Guidelines

A useful algorithm based on the National Osteoporosis Foundation (NOF) guidelines was developed by Chien and Goss.²⁸ Under this algorithm, all patients on adjuvant AIs are required to have a thorough history and physical examination focusing on prior fractures, family history of fractures and height decrease and undergo a baseline BMD and annual height measurements, in addition to lifestyle modifications. Lifestyle modifications recommended include the following: total calcium intake of 1200 to 1500 mg/day, vitamin D3 supplementation of 800 U/day, weight-bearing exercises, moderate alcohol consumption (1 to 2 drinks/day) and smoking cessation. Subsequent management is based upon the T-score as follows:

- T-score $>-1 \rightarrow$ rescreen in 1 year. If 1-year T-score >-1.0 , screen every 1 to 2 years.
- T-score between -1.0 and -1.5 $\rightarrow$ annual screening.
- T-score between -1.5 and -2.0 $\rightarrow$ check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors (advanced age, female sex, personal history of fracture as an adult, history of fracture in a first-degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, excessive alcohol consumption [>2 drinks/day], low body weight, estrogen deficiency [early menopause, menopause, bilateral ovariectomy, prolonged amenorrhea of >1 year], lifelong low calcium intake, vitamin D deficiency, chronic illness [i.e. hyperthyroidism, hyperparathyroidism, inflammatory bowel disease]).
- T-score $<-2.0 \rightarrow$ check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.

However, it remains unclear whether a particular bisphosphonate is superior.

Cost-effectiveness Analyses

Using a Markov state transition model in a hypothetical cohort of women aged 60 years with hormone receptor-positive early breast cancer starting a 5-year course of adjuvant AI, a policy of baseline and annual BMD screening followed by selective treatment with oral bisphosphonates for those diagnosed with osteoporosis was found to be the most cost-effective use of societal resources. Incremental cost-effectiveness ratio (ICER) for annual BMD screening followed by oral bisphosphonates for those with osteoporosis, annual BMD screening followed by oral bisphosphonates for those with osteopenia, and universal treatment with oral bisphosphonates were US\$87,300, US\$129,300, and US\$283,600 per quality-adjusted life year (QALY) gained, respectively.³⁹ Results were sensitive to age at AI initiation, post-treatment residual effects of oral bisphosphonates, types of bisphosphonates, and a potential adjuvant benefit of intravenous bisphosphonates. Analysis of intravenous bisphosphonates use increased the ICERs for all strategies to more than USD \$100,000 per QALY gained, but if potential of breast cancer recurrence reduction was considered, its use became more cost-effective, regardless of its impact on bone health.

Local data for cost-effectiveness analysis is not available at present.

Recommendations Regarding the Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant AIs in Breast Cancer

Systematic Recommendations (Table 1)

The SCAN workgroup voted 10 to 2 in favour of the adoption of the treatment algorithm based on the NOF guidelines as this approach gives a comprehensive recommendation based upon lifestyle modifications, inclusion of osteoporosis risk factors in decision-making, and stratification of management based on T-score.

Two members supported the NCCN recommendations which state that the use of a bisphosphonate is generally a preferred intervention to improve BMD. One agreed that the use of bisphosphonates is generally a preferred intervention to improve BMD in women with early stage breast cancer. However, limited data on their effect on fracture rates in these patients exists, hence the choice of NCCN guidelines to reflect some uncertainties regarding optimal use of bisphosphonates. The other member preferred the flexibility the NCCN guidelines offered, in particular with regard to vitamin D testing, BMD evaluations and treatment. The optimal duration of bisphosphonate has not been established. Factors to consider include BMD, response to therapy, and risk factors for continued bone loss or fracture.

The workgroup acknowledges that there are no guidelines

Table 1. Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

Guideline Recommendations	
Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant Aromatase Inhibitors in Breast Cancer	National Osteoporosis Foundation Guidelines: History and physical examination, baseline bone mineral density (BMD) and annual height measurements, lifestyle modifications. T-score >-1: Rescreen in 1 year. If 1-year BMD >-1.0, screen every 1 – 2 years. T-score between -1.0 and -1.5: annual screening. T-score between -1.5 and -2.0: check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors. T-score <-2.0: check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.
Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes	European Society for Medical Oncology (ESMO) Guidelines: Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A). Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).

on the specific choice of bisphosphonate agent. Of note, the role of denosumab has only been addressed in the ESMO 2014 guidelines as it is a relatively newer agent on the market and hence is not covered in this edition of recommendations.

There are no unsystematic recommendations.

The workgroup acknowledges that local data regarding the use of bisphosphonates to preserve bone health in postmenopausal women initiating adjuvant AIs in breast cancer is lacking.

2. Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes

Evidence on the antitumour effects of adjuvant bisphosphonates has been conflicting. Early trials using adjuvant clodronate for 2 or 3 years in breast cancer patients failed to show a beneficial antitumour effect.^{40,41} The study by Saarto et al showed adjuvant clodronate to result in inferior 10-year DFS compared to control (45% vs 58%, $P = 0.01$);⁴⁰ while the NSABP B-34 trial showed no DFS benefit from adjuvant oral clodronate at a median follow-up of 90 months although interestingly, clodronate appeared to benefit women ≥ 50 years in secondary endpoints such as recurrence-free interval (0.75, $P = 0.045$), bone metastasis-free interval (0.62, $P = 0.027$), and non-bone metastasis-free interval (0.63, $P = 0.014$).⁴¹ Similarly, in the German Adjuvant Intergroup Node-positive (GAIN) trial, there was no reported difference in DFS between early breast cancer patients randomised to oral ibandronate at 50 mg daily versus standard of care for 2 years.⁴²

The ZO-FAST and Z-FAST studies, although not powered to study zoledronate as an adjuvant treatment, found conflicting results for their secondary endpoint of DFS, with the ZO-FAST study reporting a decrease in incidence of 5-year DFS events by 34% in the upfront compared to

the delayed group (HR = 0.66; 95% CI, 0.44 to 0.97; $P = 0.0375$)³⁸ and the Z-FAST study showing similar disease recurrence and deaths between the 2 groups at 5 years of follow-up.³⁷

The AZURE study investigating the role of adjuvant zoledronate over 5 years versus standard care in stage II and III breast cancer patients found no significant difference in the primary endpoint of DFS at a median follow-up of 5 years.^{22,43} Notably, both pre- and postmenopausal women were included. Of interest, a prespecified subgroup analysis showed a possible invasive-DFS benefit (HR = 0.77; 95% CI, 0.63 to 0.96) in those who had undergone menopause >5 years earlier.⁴³ The hazard ratios for overall survival were 0.81 (95% CI, 0.63 to 1.04) for this group compared to 1.04 (95% CI, 0.86 to 1.25) for those who were less than 5 years since menopause.

However, an earlier ABCSG-12 study by Gnant et al using adjuvant zoledronate every 6 months for 3 years in premenopausal women with HR-positive early breast cancer randomised to tamoxifen/goserelin or anastrozole/goserelin with or without zoledronate showed an absolute reduction of 3.2% and a relative reduction of 36% in the risk of disease progression (HR 0.64; $P = 0.01$) but no significant reduction in the risk of death.⁴⁴ This benefit was maintained in a subsequent updated analysis at 62 months follow-up.¹⁹ Only 5% of women in the ABCSG-12 study had prior chemotherapy, compared to about 95% in the AZURE study.

The recent EBCTCG meta-analyses examining the role of adjuvant bisphosphonates in early breast cancer, consisting of 18,766 women, mostly those in trials of 2 to 5 year of bisphosphonates, demonstrated that it produced highly significant reductions in recurrence (RR = 0.86; 95% CI, 0.78 to 0.94; $2P = 0.002$), distant recurrence (0.82; 0.74 to 0.92; $2P = 0.0003$), bone recurrence (0.72; 0.60 to 0.86, $2P = 0.0002$) and breast cancer mortality (0.82; 0.73 to 0.93;

2P = 0.002) among postmenopausal (natural or induced) women when treatment began; the effect of which was not similarly seen in premenopausal women.²¹ Only the preliminary results of the EBCTCG meta-analyses had been incorporated into the ESMO guidelines we reviewed.

The literature is still unclear with regards to the exact choice of bisphosphonates, the optimal dosing and duration of therapy.

Cost-effectiveness Analyses

In a recent cost-effectiveness analysis study of adjuvant bisphosphonates in a simulated cohort of 100,000 postmenopausal women with non-metastatic breast cancer followed over 10 years using available clinical trials and meta-analysis data, alendronate at 70 mg/week and ibandronate at 150 mg/month were cost saving compared to no therapy, while zoledronic acid at 4 mg/6 months had an ICER of USD \$10,317/QALY gained.⁴⁵ High-dose ibandronate at 50 mg/day and high-dose zoledronate (6 doses in the first 6 months, 8 doses in the next 24 months and 5 doses in the final 30 months) were not cost-effective at a willingness-to-pay threshold of \$50,000/QALY gained.

Local data for cost-effectiveness analysis is not available at present.

Recommendations Regarding the Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes

Systematic Recommendations (Table 1)

The SCAN Workgroup voted unanimously in support of the ESMO 2014 guidelines which state that adjuvant bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A), but they do not improve disease outcomes in premenopausal women (I, A). The collective opinion from the members was in line with these recommendations that offering adjuvant bisphosphonates is justified in the postmenopausal but not premenopausal setting.

There are no unsystematic recommendations.

The workgroup acknowledges that local data regarding the use of adjuvant bisphosphonates to improve breast cancer outcomes is lacking.

Conflicts of Interest

Dr Dent reports receiving advisory board fees from Roche; Dr Shang, honoraria from Novartis; Dr Ang, Dr Khoo, Dr Lee, Dr Lim, Dr Ng, Dr Shih, Dr Tan, Dr Wong, Dr Wong and Dr Yap have nothing to disclose.

Workgroup Members

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Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fatima Cardoso, MD, Breast Unit, Champalimaud Clinical Center, Portugal.

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Supplementary Table 1. International Guidelines for the Use of Bisphosphonates for Bone Health When Using Adjuvant Aromatase Inhibitors

Guideline Title	Algorithm Based on Guidelines from National Osteoporosis Foundation	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3.2015	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment Full Guideline	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least 2/3rds of Workgroup Concur)
Date Released	November 2006	July 2015	April 2014	February 2009	September 2013	April 2014	April 2014
Guideline Developer	Chien and Goss. JCO 2006; 24:5305	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Scottish Intercollegiate Guidelines Network (SIGN)	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	NA	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines approved by the ESMO Guidelines Working Group: March 2014.	Guideline development group made up of health professionals, representatives of patient and carer groups, and technical experts assess the available evidence and make recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	SIGN guidelines are developed using an explicit methodology. - Development is carried out by multidisciplinary, nationally representative groups. - A systematic review is conducted to identify and critically appraise the evidence. - Recommendations are explicitly linked to the supporting evidence.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.
Target Population	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer
Bisphosphonates for Osteoporosis Prevention	History and physical examination, baseline BMD and annual height measurements, lifestyle modifications. T-score >-1: rescreen in 1 year. If 1-year BMD >-1: screen every 1-2 years. T-score between -1.0 and -1.5: annual screening.	The use of a bisphosphonate is generally a preferred intervention to improve BMD. Optimal duration of bisphosphonate has not been established. Factors to consider include BMD, response to therapy, and risk factors for continued bone loss or fracture.	Bisphosphonates and denosumab prevent bone loss associated with use of ovarian suppression or aromatase inhibitors in early breast cancer (1B).	Qualifying statement: This recommendation is based on evidence from RCTs and guidance produced by Reid et al (2008). Guidance for the management of breast cancer treatment-induced bone-loss: A consensus position statement from a UK Expert Group. Cancer Treatment Reviews. Volume 34 (Suppl 1), S3-S18.	Women who are postmenopausal and on AIs – High risk: T-score <-2 or known vertebral fracture > Bisphosphonates and calcium and vitamin D. Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months.	Algorithm based on guidelines from National Osteoporosis Foundation (Chien and Goss. JCO 2006; 24:5305)	NA

AI: Aromatase inhibitors; BMD: Bone mineral density; BMI: Body mass index; DXA: Dual energy X-ray absorptiometry; NA: Non-applicable; RCT: Randomised controlled trials; TH: Total hip

Supplementary Table 1. International Guidelines for the Use of Bisphosphonates for Bone Health When Using Adjuvant Aromatase Inhibitors (Con't)

Guideline Title	Algorithm Based on Guidelines from National Osteoporosis Foundation	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3.2015	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment Full Guideline	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least 2/3rds of Workgroup Concur)
				Women who are postmenopausal and on AIs – High risk: T-score ≤ -2 or known vertebral fracture > Bisphosphonates and calcium and vitamin D. Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months. Medium risk: T-score between -1 and -2 Lifestyle advice plus calcium and vitamin D. Repeat axial BMD after 24 months. If annual rate of bone loss $>4\%$ at LS or TH and /or T-score ≤ -2.0 > bisphosphonates and treat under high risk category. Low risk: Both T-scores > -1 . Lifestyle advice. Women ≥ 75 years old with at least 1 major risk factor (previous low trauma fracture >50 years old, parental history of hip fracture, alcohol intake ≥ 4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, BMI <22): Bisphosphonates and calcium and vitamin D.			
	T-score between -1.5 and -2.0 : check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors. T-score ≤ -2.0 : check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.			Women ≥ 75 years old with at least one major risk factor (previous low trauma fracture >50 years old, parental history of hip fracture, alcohol intake ≥ 4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, BMI <22): Bisphosphonates and calcium and vitamin D.			
Member Votes	10 out of 12 votes	2 out of 12 votes	Nil	Nil	Nil	10 out of 12 votes	NA

AI: Aromatase inhibitors; BMD: Bone mineral density; BMI: Body mass index; DXA: Dual energy X-ray absorptiometry; NA: Non-applicable; RCT: Randomised controlled trials; TH: Total hip

Supplementary Table 2. International Guidelines for the Use of Adjuvant Bisphosphonates to Influence Breast Cancer Outcomes

Guideline Title	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	BC Cancer Agency: Breast Cancer Management. Miscellaneous Considerations	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least Two-thirds of Workgroup Concur)
Date Released	April 2014	January 2013	April 2014	April 2014
Guideline Developer	European Society for Medical Oncology (ESMO)	BC Cancer Agency	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines approved by the ESMO Guidelines Working Group: March 2014.	The BC Cancer Agency has prepared these cancer management guidelines, based on the accumulated experiences of this agency together with "best" practice evidence derived from major cancer centres throughout the world. The recommendations have been developed by provincial tumour groups composed of oncologists, radiologists, pathologists, oncology nurses, pharmacists and practitioners from health disciplines contributing to specialised oncology care at the BC Cancer Agency and University of British Columbia.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.
Target Population	Early breast cancer	Early breast cancer		
Bisphosphonates as Adjuvant Therapy	Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A). Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).	There is insufficient evidence to routinely recommend bisphosphonate therapy to adjuvant breast cancer patients. Oncologists may recommend intermittent zoledronic acid for three years in selected early breast cancer patients based on existing evidence.	ESMO Clinical Practice Guidelines	NA
Member Votes	12 of 12 votes	Nil	12 of 12 votes	NA