# BONE HEALTH
# IN PATIENTS WITH BREAST CANCER

Effective Date: November 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

## BACKGROUND

Optimization of bone health is an important aspect to consider for patients with a breast cancer diagnosis at any stage. In patients with early stage breast cancer, treatment associated bone loss can occur either with adjuvant endocrine therapy (e.g. aromatase inhibitors), or in patients with a loss of ovarian function due to surgery or chemotherapy. Bone loss in this setting is due to enhanced bone turnover secondary to estrogen decline. [1] Other factors, unrelated to breast cancer, that may also contribute to the risk of bone loss, include age (>65 years), race (Caucasian), low body mass index (<20 kg/m$^2$), family and personal history of fractures, menopausal status, oral corticosteroid use, history of osteoporosis, and smoking. [2] In the early stage breast cancer setting, bone loss can present (as is the case with osteopenia or osteoporosis) as bone fractures, bone pain, and/or impaired mobility. The rate of vertebral fractures is five times higher among women with breast cancer, as compared to the general population. [3] As such, there is an impact on overall quality of life for these patients.

Bone health can also be compromised in the metastatic breast cancer setting, as a result of malignant cells stimulating bone resorption via osteoclasts; this break down of bone then signals further tumour growth, leading to increased risk of skeletal related events such as pain, morbidity, spinal compression and hypercalcemia. [4,5] Among patients with metastatic breast cancer, the incidence of bone metastases is approximately 73%. [6] In 2011 there were an estimated 2,100 new cases of female breast cancer in Alberta; [7] this translates into 105 new cases of metastatic breast cancer, [8] of which 77 will present with bone metastases. The prevalence of patients with bone metastases is even higher. [6]

To date, efforts to optimize bone health have focused on bisphosphonates and biological agents, such as denosumab. Although the effectiveness of bone modifying agents (BMAs) in improving bone health has been well established, uncertainties still remain (e.g. ideal time to initiate therapy, duration of therapy, modification of therapy, etc.). The purpose of this guideline is to provide evidence-based strategies for the management of bone loss and symptoms of bone loss in patients with a breast cancer diagnosis.

## GUIDELINE QUESTIONS

### *Patients with Metastatic Breast Cancer*

1. When should bone modifying agents (BMAs) be used in patients with metastatic breast cancer?
2. Which BMAs should be considered and for how long?
3. Should the BMA be switched after a skeletal-related event (SRE) or documentation of disease progression in bone?

### *Patients with Early Stage Breast Cancer*

4. How should fracture risk be assessed and when for:
   - premenopausal women with premature ovarian failure or ovarian suppression with luteinizing hormone releasing hormone analogue (LHRHA)
   - postmenopausal women on aromatase inhibitors (AIs)
   - other postmenopausal women with early stage breast cancer
5. Is there a role for BMAs in these populations and, if so, which agents should be considered and for how long?
6. How should treatment with BMAs be monitored for effectiveness?

7. Should BMAs be used as adjuvant therapy to improve breast cancer-related outcomes?

***Patients with Metastatic or Early Stage Breast Cancer***

8. When using BMAs, what potential adverse events should be disclosed to patients? What is the frequency of these adverse events with the different agents and schedules of administration? How should these adverse events be managed?

## DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgeons, pathologists, psychosocial oncologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a knowledge management specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit handbook.

This guideline was drafted by a medical oncologist with expertise in the area of bone health and breast cancer, with support from a knowledge management specialist. An expert panel consisting of medical oncologists, radiation oncologists, breast surgeons, and pathologists then reviewed the guideline and came to consensus on the recommendations.

This guideline was originally developed in November 2012.

## SEARCH STRATEGY

A systematic search for relevant literature related to breast cancer and bone health was conducted of: MEDLINE (1950 to 2011 July) and EMBASE (1980 to 2012 July). The search included the terms *zoledronic acid* or *zoledronate* or *clodronate* or *clodronic acid* or *alendronate* or *alendronic acid* or *pamidronate* or *pamidronic acid* or *ibandronate* or *ibandronic acid* or *denosumab* and *breast neoplasm*. The MEDLINE and EMBASE search was limited to clinical trials, phase III, randomized controlled trials, and meta-analyses published in the English language.

Studies that were published prior to 1996 were excluded from the evidence tables. A total of 28 clinical trials were deemed relevant to the role of bisphosphonates and denosumab in the prevention of skeletal related events in patients with metastatic breast cancer; 11 clinical trials were deemed relevant to the role of bisphosphonates or denosumab in preventing recurrence or prolonging survival in metastatic breast cancer; and 21 clinical trials were deemed relevant to the role of bisphosphonates or denosumab for the treatment of hypercalcemia of malignancy in metastatic breast cancer.

In addition, the National Guidelines Clearinghouse was searched for guidelines and systematic reviews related to breast cancer and bone health. A total of seven clinical practice guidelines that provided recommendations on the use of bisphosphonates in the setting of breast cancer were deemed relevant; these guidelines were developed by: ASCO, [9,10] the National Comprehensive Cancer Network (NCCN), [11] Cancer Care Ontario (CCO), [12] the British Columbia Cancer Agency (BCCA), [13] the International Society of Geriatric Oncology (ISGO), [14] the European Expert Panel (EEP), [15] and Cancer Australia. [16] Following the initial literature search, an additional Canadian guideline, BONUS 6, was published by a panel of experts in the field [17] and ASCO released an updated version of their guideline. [18]

## TARGET POPULATION

This guideline was developed for medical oncologists, radiation oncologists, breast surgeons, nurse practitioners, and family physicians or general oncologists involved in the care of patients with breast cancer. The recommendations in this guideline apply to patients who have been diagnosed with breast cancer and in whom bone metastases have been confirmed or for those at risk of therapy-induced bone loss. Similar guidance may exist for patients with other malignancies, such as prostate cancer or multiple myeloma, who may also experience bone metastases and therapy-induced bone loss; however, the following recommendations apply specifically to patients with breast cancer.

## SUMMARY OF RECOMMENDATIONS

### *Patients with Metastatic Breast Cancer*

1. **When to use bone-modifying agents.** In patients with metastatic breast cancer, bone modifying agents (BMAs) are recommended upon confirmation of bone metastases; the presence of non-bone metastases is not an indication for the use of bone modifying agents.

2. **Which BMAs to consider and for how long.**
   - For patients with breast cancer with bone metastases, no recommendations can be made favoring one agent over another. Acceptable agents and dosing regimens for bone metastases include:
     - Zoledronic acid: intravenous (IV) 4 mg over no less than 15 minutes, monthly
     - Pamidronate: IV 90 mg over no less than 2 hours, monthly
     - Clodronate: oral 1600 mg, daily
     - Denosumab: subcutaneous (SC) 120 mg, monthly

     Note: There are advantages and limitations to the different agents and routes of administration. The agent and route of administration should be left to the discretion of the treating physician, taking into account compliance with treatment, cost of treatment, and patient preference.
   - BMAs should be continued in patients with breast cancer with bone metastases until there is evidence of a substantial decline in performance status.

3. **What to do after a SRE or disease progression in bone.** In patients with breast cancer with bone metastases, who have experienced a skeletal-related event (SRE) or progression in bone metastases, switching from one BMA to another is currently not recommended, as there is no double-blind data to support this strategy.

### *Patients with Early Stage Breast Cancer*

4. **Fracture risk assessment and timing.**
   - Baseline bone mineral density (BMD) testing and fracture risk assessment is recommended for patients with early stage breast cancer for whom therapy with agents that suppress ovarian function is planned, including:
     - premenopausal women with premature ovarian failure or ovarian suppression with luteinizing hormone releasing hormone analogue (LHRHA)
     - postmenopausal women on aromatase inhibitors (AIs)
   - BMD testing in other postmenopausal women with early stage breast cancer is recommended according to the indications provided in Table 1 (Canadian Osteoporosis screening guidelines [19]).

- BMD is calculated using a dual-energy x-ray absorptiometry (DEXA) scan.
- Fracture risk should be assessed using the World Health Organization Fracture Risk Assessment Tool (FRAX; www.shef.ac.uk/FRAX/tool.jsp?locationValue=9).
- Repeat BMD testing should be performed as follows, in patients for whom pharmacotherapy with bone modifying agents is deemed to be not beneficial:
  - low risk patients (10-year risk <10% based on FRAX score): every five years
  - moderate risk patients (10-year risk 10-20% based on FRAX score): every one to three years

**Table 1.** Canadian guidelines on the screening of osteoporosis (*reproduced with permission from A. Papaioannou*). [19]

| **Indications for measuring bone mineral density** | |
|---|---|
| ***Older adults (age ≥50 years)*** | ***Younger adults (age < 50 years)*** |
| Age ≥ 65 yr (both women and men) | Fragility fracture |
| Clinical risk factors for fracture (menopausal women, men age 50–64 years) | Prolonged use of glucocorticoids * |
| Fragility fracture after age 40 years | Use of other high-risk medications † |
| Prolonged use of glucocorticoids* | Hypogonadism or premature menopause (age <45 years) |
| Use of other high-risk medications † | Malabsorption syndrome |
| Parental hip fracture | Primary hyperparathyroidism |
| Vertebral fracture or osteopenia identified on radiography | Other disorders strongly associated with rapid bone loss and/or fracture |
| Current smoking | |
| High alcohol intake | |
| Low body weight (<60 kg) or major weight loss (>10% of body weight at age 25 years) | |
| Rheumatoid arthritis | |
| Other disorders strongly associated with osteoporosis | |

* At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily.
† For example, aromatase inhibitors or androgen deprivation therapy.

**5. When to use BMAs, which agents to consider, and for how long.**

- BMAs should be considered for the following patients with early stage breast cancer:
  - premenopausal OR postmenopausal at high risk (i.e., 10-year fracture risk >20% OR prior fragility fracture of hip or spine OR more than one fragility fracture)
  - postmenopausal at moderate risk (i.e., 10-year fracture risk 10%–20%) OR a T-score less than -2.0, AND undergoing aromatase inhibitor therapy for breast cancer
- As per the Canadian Osteoporosis guidelines, [19] exercise, adequate calcium (1,200 mg per day total, diet plus supplements) intake, and vitamin D (1,000 IU per day) supplementation are also recommended.
- For patients with early stage breast cancer, no recommendations can be made favoring one bone modifying agent over another. Acceptable agents and dosing regimens for bone loss include:
  - Zoledronic acid: IV 4 mg over no less than 15 minutes every 6-12 months
  - Any oral bisphosphonate
  - Denosumab: SC 60 mg every 6-12 months

Note: the route of administration should be left to the discretion of the treating physician, taking into account compliance with treatment, cost of treatment, and patient preference.

- There is no data on the optimal duration of therapy with bone-modifying agents for patients with early stage breast cancer with treatment-related bone loss. Most randomized controlled trials have used durations of two to three years and none have compared one time period with another.
- In patients with early stage breast cancer, there is no data to support a switch from one agent to another, following a skeletal-related event.

6. **Monitoring for effectiveness.** In patients with early stage breast cancer undergoing therapy with a bone modifying agent, BMD can be checked every two years. However, in patients with osteopenia, BMD should be checked annually.

7. **Use of BMAs as adjuvant therapy.** Outside of a clinical trial, bone modifying agents are not recommended, for patients with early stage breast cancer, as a standard adjuvant therapy to improve recurrence or survival rates.

***Patients with Metastatic or Early Stage Breast Cancer***

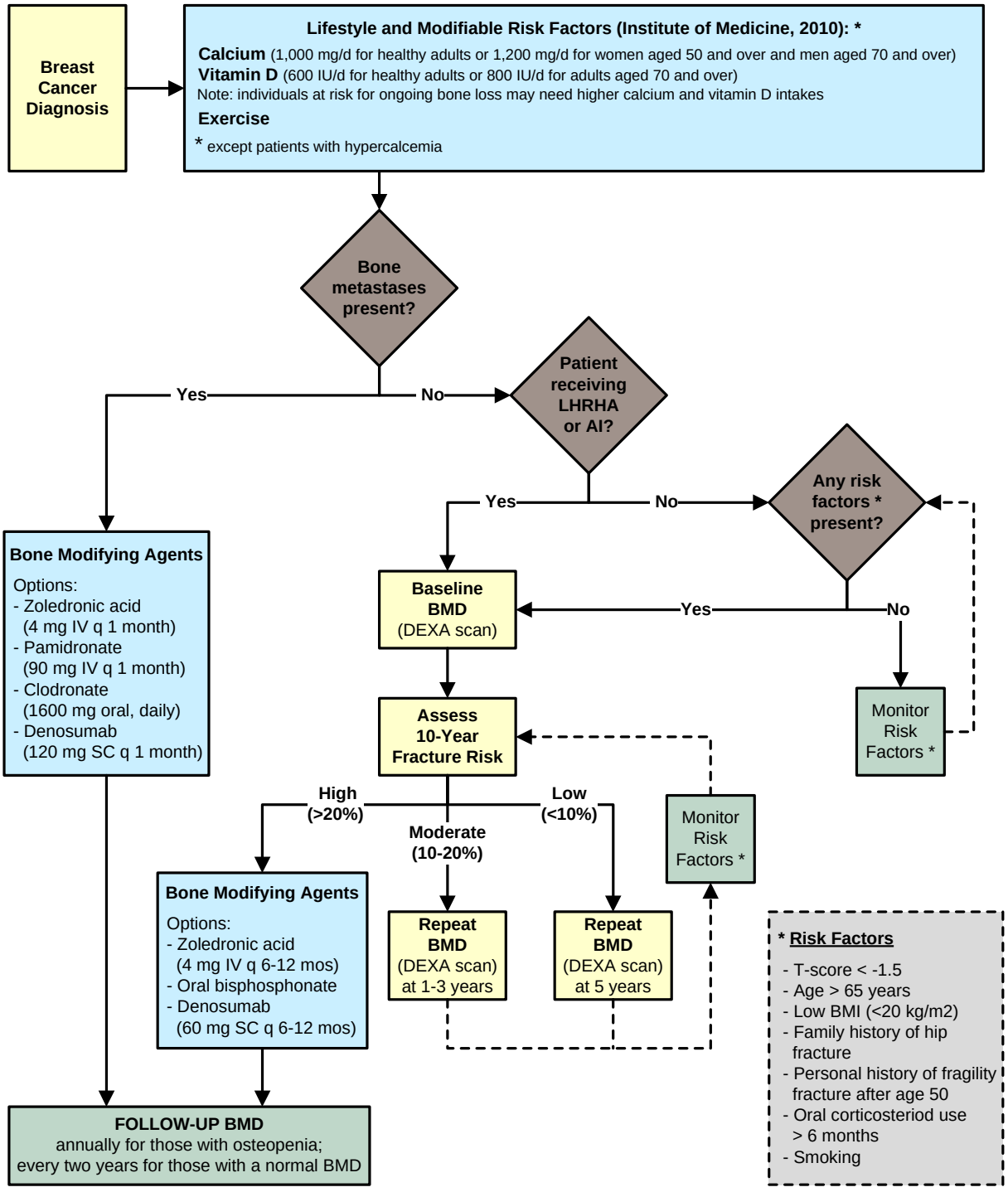
8. **Monitoring of adverse events.** Patients undergoing therapy with BMAs should be aware that the most common adverse events include nausea, fatigue, arthralgia, back pain, pyrexia, bone pain, vomiting, anemia, diarrhea, dyspnea, extremity pain, and constipation (Table 2).

**Table 2.** Adverse events associated with the use of BMAs.

| Adverse event | Zoledronate 4 mg IV q 1 mo (% frequency) | Pamidronate 90 mg IV q 1 mo (% frequency) | Clodronate 1600 mg oral, daily (% frequency) | Denosumab 120 mg SC q 1 mo (% frequency) |
|---|---|---|---|---|
| Nausea | 38-44 | 44 | 27 | 35 |
| Fatigue | 32-39 | 38 | rate not reported | 30 |
| Arthralgia | 22-29 | 17 | rate not reported | 25 |
| Back pain | 26 | rate not reported | rate not reported | 24 |
| Pyrexia/fever | 24-36 | 29 | rate not reported | 17 |
| Bone pain | 24-55 | 55 | rate not reported | 18 |
| Vomiting | 24-30 | 30 | 15 | 21 |
| Anemia | 23-27 | 28 | rate not reported | 19 |
| Diarrhea | 20-25 | 25 | 20 | 23 |
| Dyspnea | 19-25 | 24 | rate not reported | 22 |
| Extremity pain | 22 | rate not reported | rate not reported | 20 |
| Constipation | 20-24 | 24 | 13 | 17 |
| Headache | 19 | 24 | rate not reported | rate not reported |
| Dyspepsia | rate not reported | rate not reported | 16 | rate not reported |

Patients should also be monitored for changes in renal function (i.e., creatinine clearance). In addition, patients with poor dental hygiene or poor dental health may be at increased risk of osteonecrosis of the jaw and should ideally consider undergoing preventive dentistry before starting treatment with a bone modifying agent. Adverse events should be managed with appropriate supportive care.

A clinical algorithm for the use of bone-modifying agents in breast cancer is presented in Figure 1.




**Abbreviations: LHRHA = luteinizing hormone releasing; AI = aromatase inhibitor; BMD = bone mineral density (DEXA scan)**

**Figure 1.** Algorithm for the use of bone modifying agents in patients with breast cancer with bone metastases or treatment-induced bone loss.

## DISCUSSION

Bone loss can occur in breast cancer due to treatment, especially estrogen suppressing therapy and certain chemotherapies, or due to the disease itself; [1,4] however, bone modifying agents such as bisphosphonates and demosumab offer patients with breast cancer with metastatic disease a way to treat and potentially prevent bone loss. The following discussion of the literature will highlight trials demonstrating the effectiveness and safety of these bone modifying agents and describe data on less established areas, such as the timing of therapy, the duration of therapy, and the use of therapy as an adjuvant to prolong survival.

### Treatment-Related Bone Loss

The effectiveness of bisphosphonates as bone modifying agents has been well established. Trials employing the use of zoledronic acid, risedronate, alendronate, ibandronate, clodronate or pamidronate in patients receiving aromatase inhibitors or chemotherapy have demonstrated that these agents increase bone mineral density and decrease bone turnover and the risk of fractures. The phase III trial ABCSG-12 demonstrated in early stage premenopausal patients (n=404) that zoledronic acid (4 mg IV, every six months) significantly increased bone mineral density at the hip and spine (+3.9% and +4.0%, respectively, versus baseline) at five years follow-up, whereas the placebo group experienced significant losses at these sites (-4.1% and -6.3%, respectively, versus baseline). [20-26] Others have observed similar changes in bone mineral density with the use of zoledronic acid among premenopausal patients. [27-29] No significant difference in the rate of fractures has been observed among the premenopausal group in any of these studies and there have been mixed results regarding the markers of bone turnover (i.e., N-terminal telopeptide [NTX], C-terminal cross-linked telopeptide of type I collagen [CTX-I], N-terminal propeptide of type I collagen [PINP], and bone alkaline phosphatase [AP]). [20-29] Of interest, the ABCSG-12 trial demonstrated a significant improvement in disease-free survival (95% CI 0.46- 0.91) and fewer recurrences at a median follow up period of five years, with zoledronic acid. Finally, pamidronate (60 mg IV, every three months), but not risedronate (35 mg per week, orally), was able to achieve a significant 1.9% increase in bone mineral density at the spine, but not at hip, among premenopausal patients undergoing chemotherapy. [30,31]

Among post-menopausal women receiving aromatase inhibitors, a variety of bisphosphonates have been tested and show similar improvements in bone loss. Zoledronic acid (4 mg IV, every six months) was shown to maintain or significantly increase (+2.66% versus baseline) bone mineral density at the spine. [32,33] Similarly, in the SABRE and ReBBeCa Trials, risedronate demonstrated significantly better maintenance or increases in bone mineral density, versus placebo (2.5-2.9% higher than placebo for hip and 1.6-4.0% higher than placebo for spine); significant improvements in NTX, CTX-I, PINP, and bone AP, indicating a reduction in bone turnover, were also observed. [34-36] The ARIBON trial likewise demonstrated improvements in bone mineral density at the hip and spine (4.5% higher than placebo for hip and 6.2% higher than placebo for spine) with ibandronate (150 mg orally, every 28 days); in addition, ibandronate improved serum levels of NTX, CTX-I, bone AP, as well as T-score. [37] Oral clodronate (1600 mg per day) also led to a significant improvement in bone mineral density at the hip, spine, and femoral neck among postmenopausal patients. [38,39] Finally, alendronate has also demonstrated efficacy among postmeno-pausal patients in maintaining or increasing bone mineral density at the spine and femoral neck. [40,41] To date, no trials comparing one bisphosphonate with another have been conducted in the setting of treatment-related bone loss; bisphosphonates are generally thought to be equal in terms of efficacy and the decision to use one agent over another is often related to route of administration or other factors that could affect compliance.

The ratio of receptor osteoprotegerin (OPG) to receptor activator of nuclear factor-kappa B ligand (RANKL) plays a role in osteoclastogenesis: when RANKL is high, bone loss will occur. However, by altering the ratio in favor of OPG by inhibiting RANKL, bone loss can be prevented. [42] Therefore, biological agents that inhibit RANKL may prevent bone loss due to treatment or metastases. Denosumab, a RANKL inhibitor, has demonstrated efficacy among postmenopausal patients receiving aromatase inhibitors. As compared to placebo, denosumab (60 mg SC, every six months) significantly increased bone mineral density of the hip (+4.7% versus placebo), spine (+7.6% versus placebo), wrist (+6.1% versus placebo), and femoral neck (+3.6% versus placebo). [43,44] In this trial, denosumab also significantly improved serum levels of CTX (-91% versus +9% for placebo) and PINP (-29% versus -2% for placebo), but did not significantly improve the rate of fractures.

Recommended agents for the prevention and management of bone loss include zoledronic acid (IV 4 mg over no less than 15 minutes every 6-12 months) and denosumab (60 mg SC every 6-12 months). Any oral bisphosphonate is acceptable as well, including clodronate (1600 mg per day), risedronate (35 mg per day), or alendronate (70 mg per day). The route of administration should be left at the discretion of the treating physician, taking into account compliance with treatment, cost of treatment, and patient preference. Denosumab, however, may be limited in its coverage by provincial health insurance plans. Alberta specific information can be found on the AHW Drug Benefit List (https://idbl.ab.bluecross.ca/idbl/load.do) when deciding on an agent.

The timing of therapy (upfront versus delayed) has been evaluated in several trials, among postmeno-pausal patients receiving aromatase inhibitors. The Z-FAST, [45-48] ZO-FAST, [49-51] and EZO-FAST [52,53] and N03CC [54,55] phase III trials compared zoledronic acid upfront (i.e., immediately) with delayed (i.e., following a fracture or a decrease in bone mineral density). Immediate zoledronic acid (4 mg IV, every six months) significantly increased bone mineral density at both the hip (5.4-6.7% higher than delayed) and the spine (8.6-9.3% higher than delayed) in the ZO-FAST and Z-FAST trials, as well as in meta-analysis of the combined data (hip: 3.4% higher than delayed; spine: 5.1% higher than delayed). [56] The EZO-FAST and N03CC trials also reported significant improvements in bone mineral density at the hip and spine. Where reported, there were no significant differences in T-scores, fracture rates, or overall survival for any of these studies.

**Cancer-Related Bone Loss**

Bone loss can occur in metastatic breast cancer as a result of malignant cells stimulating bone resorption, which in turn signals further tumour growth. [4] Bone modifying agents may, therefore, be able to reverse bone loss in patients with bone metastases. In two trials, both comparing clodronate (1600 mg per day, orally) with placebo for two or three years duration, among patients with breast cancer bone metastases, no significant differences in favor of clodronate were found for disease-free survival, overall survival, or the rate of new bone metastases. [57-62] However, zoledronic acid (4 mg IV, every four weeks) was shown to significantly decrease the fracture rate (25.4% versus 38.9% for placebo) and lower the incidence of one or more skeletal related events (29.8% versus 49.6% for placebo) among breast cancer patients with bone metastases. [63] Likewise, pamidronate (90 mg IV every three to four weeks for 24 cycles) significantly decreased the fracture rate (40% versus 52% for placebo), the level of bone AP (-33% versus +5% for placebo), and the incidence of one or more skeletal related events (51% versus 64% for placebo). [64] Similar significant positive changes in the fracture rate and incidence of skeletal related events were observed for ibandronate (2 or 6 mg every three to four weeks). [65,66] Zoledronic acid, pamidronate, and ibandronate were then compared with denosumab and demonstrated similar efficacy, in terms of overall

survival, at six months, among breast cancer patients with bone metastases (85% for denosumab versus 81% for bisphosphonates). [67]

In summary, bone modifying agents are recommended for patients with breast cancer with evidence of bone metastases. The presence of non-bone metastases is not an indication for the use of bone modifying agents; however the bone modifying agents should be used when osteopenia (i.e., T-score between -1.0 and -2.5) or osteoporosis (i.e., T-score less than -2.5) is present. Recommendations can not be made, favoring one agent over another. Acceptable agents and dosing regimens for bone metastases include zoledronic acid (4 mg IV over no less than 15 minutes every 4 weeks), pamidronate (90 mg IV over no less than 2 hours every 3 to 4 weeks), clodronate (1600 mg per day orally), and denosumab (120 mg SC every four weeks). There are several advantages and limitations to the different agents and routes of administration. The route of administration should be left to the discretion of the treating physician, taking into account compliance with treatment, cost of treatment, and patient preference. Denosumab, however, may be limited in its coverage by provincial health insurance plans.

**Bone Modifying Agents as Adjuvant Therapy**

The use of bone modifying agents as an adjuvant to standard therapy has also been investigated. Clodronate (1600 mg per day, orally) taken over a duration of two years significantly improved overall survival (81.5% versus 76.1% for placebo) and reduced the incidence of bone metastases (9.6% versus 13.5% for placebo) among patients with primary operable breast cancer. [68,69] However, pamidronate (150 mg per day, orally) did not improve overall survival or the rate of bone metastases, versus placebo. [70] Similarly, among patients with breast cancer (stages II-III) with bone metastases in the AZURE trial, zoledronic acid (4 mg every 3-4 weeks for six doses, followed by surgery, followed by 4 mg every 3 months for eight doses and then every 6 months for five doses) did not improve disease-free survival (77% versus 77%) or overall survival (85.4% versus 83.1%) as compared to standard therapy; however, a post-hoc analysis of premenopausal patients revealed a significant improvement with treatment. [71,72] The NSABP B-34 trial recently published the 7.5 year (median 90.7 months follow up) analysis of survival data among early breast cancer patients treated with oral clodronate (1600 mg per day) for three years or placebo. [73] Overall, evidence for the use of bisphosphonates as adjuvant therapy for prevention of bone metastases in women with breast cancer is weak and further study in this setting is warranted. Ongoing research includes the D-CARE trial, which randomizes patients with bone metastasis to denosumab or placebo and follows patients for the main outcomes of disease-free survival and bone metastasis-free survival. [74] Until such data is available, the use of bone modifying agents is not recommended, outside of a clinical trial, for patients with breast cancer as a standard adjuvant therapy to improve recurrence or survival rates.

**Toxicity and Side Effects**

Adverse events associated with bisphosphonate use (oral or intravenous) and demosumab are typically mild and manageable, but include arthralgia, fever, thrombosis, bone pain, fatigue/tiredness, nausea, and gastrointestinal symptoms. [23,27,31,34,43,44,67] A table providing the frequencies of the most common adverse events is provided in Table 2. Patients undergoing therapy with bone modifying agents should be monitored throughout therapy for changes in renal function (i.e., creatinine clearance). [11,75-77] In addition, patients with poor dental hygiene or poor dental health may be at increased risk of osteonecrosis of the jaw; [78,79] therefore, patients should consider undergoing preventive dentistry before starting treatment with a bone modifying agent and avoid extensive dental work during therapy. [11]

## GLOSSARY OF ABBREVIATIONS

| Acronym | Description |
|---|---|
| AHS | Alberta Health Services |
| AI | aromatase inhibitor |
| AP | bone alkaline phosphatase |
| ASCO | American Society of Clinical Oncology |
| BCCA | British Columbia Cancer Agency |
| BMA | bone modifying agent |
| BMD | bone mineral density |
| CCO | Cancer Care Ontario |
| CTX-I | C-terminal cross-linked telopeptide of type I collagen |
| DEXA | dual-energy x-ray absorptiometry |
| EEP | European Expert Panel |
| ISGO | International Society of Geriatric Oncology |
| IV | intravenous |
| NTX | N-terminal telopeptide |
| OPG | osteoprotegerin |
| PINP | N-terminal propeptide of type I collagen |
| RANKL | receptor activator of nuclear factor-kappa B ligand |
| SC | subcutaneous |
| SRE | skeletal related event |

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2014. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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## APPENDIX: EVIDENCE TABLES

**Table 1A. Trials reporting BONE MINERAL DENSITY (BMD) for a bone-modifying agent versus placebo among patients at risk of TREATMENT-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration (Y)* | *Follow-up (M)* | *Patients (N)* | *Menopause (%)* | *Treat-ment* | *BMD, hip (% change)* | *BMD, spine (% change)* | *BMD, wrist (% change)* | *BMD, femoral neck (% change)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Van Poznak C. (SABRE) 2010 | Risedronate<br>Placebo | 35 mg/wk oral | 1 | 24 | 77<br>77 | 100<br>100 | AI | +1.80%*<br>-1.10% | +2.2%*<br>-1.8% | NR | NR |
| Gnant M. 2009 (ABCSG12) | Zoledronic acid<br>No treatment | 4 mg IV q 6 mo | 3 | 60 | 205<br>199 | 0 | AI | +3.9%<br>-4.1% | +4.0%*<br>-6.3%* | NR | NR |
| Ellis GK. 2009 | Denosumab<br>Placebo | 60 mg sc q 6 mo | 2 | 24 | 127<br>125 | 100<br>100 | AI | +4.7%<br>vs. placebo | +7.6%<br>vs. placebo | +6.1%<br>vs. placebo | +3.6%<br>vs. placebo |
| Lester JE. 2008 (ARIBON) | Ibandronate<br>Placebo | 150 mg oral q 4w | 2 | 24 | 25<br>25 | 100<br>100 | AI | +0.60%*<br>-3.90% | +2.98%*<br>-3.22% | n/a<br>n/a | n/a<br>n/a |
| Safra T. 2009 | Zoledronic acid<br>Control | 4 mg IV q 6 mo | 2 | 18.2 | 33<br>39 | 100<br>100 | AI | NR | maintained<br>declined* | NR | NR |
| Hines S. 2009 | Zoledronic acid | 4 mg IV q 6 mo | 5 | 12 | 60 | 100 | AI | NR | +2.66%* | NR | +4.81%* |
| Cohen A. 008 | Alendronate<br>Placebo | 70 mg/wk oral | 1 | 12 | 6<br>5 | 100<br>100 | AI | NR | NR | NR | +0.1%*<br>-5.2% |
| Saarto T. 1997 | Clodronate<br>Placebo | 1600 mg/d oral | 2 | 24 | 44<br>49 | 100<br>100 | CT | NR | -5.5%<br>-10.3% | NR | -5.2%<br>-7.2% |
| Delmas PD. 1997 | Risedronate<br>Placebo | 30 mg/d oral x 14 then q 12 wk | 2 | 36 | 27<br>26 | 100<br>100 | CT | NR | +2.8%*<br>vs. placebo | NR | +3.4%*<br>vs. placebo |
| Hines SL. 2009 (N02C1) | Risedronate<br>Placebo | 35 mg/wk oral | 1 | 12 | 106<br>106 | 0<br>0 | CT | -2.7%<br>-3.4% | -4.3%<br>-5.4% | NR | -2.2%<br>-2.4% |
| Fuleihan GH. 2005 | Pamidronate<br>Placebo | 60 mg IV q 3 mo | 1 | 12 | 21<br>19 | 0<br>0 | CT | -0.3%<br>-2.8% | +1.9%*<br>-3.2% | NR | NR |
| Ahn JH. 2009 | Zoledronic acid<br>No treatment | 4 mg IV q 6 mo | 1 | 12 | 55<br>55 | 0<br>0 | CT | NR | +1.0%*<br>-7.5% | NR | +3.6% *<br>vs. no treatment |

**Table 1B. Trials reporting BONE TURNOVER for a bone-modifying agent versus placebo among patients at risk of TREATMENT-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration* | *F/U (M)* | *Pts (N)* | *Fractures* | *N-telopept.* | *C-term. telo* | *T >-1* | *PINP* | *Bone ALP* | *SRE* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Van Poznak C. (SABRE) 2010 | Risedronate<br>Placebo | 35 mg/wk oral | 1 yr | 24 | 77<br>77 | 0%<br>0% | NR | -43.8%*<br>+6.1% | NR | -44.3%*<br>-2.4% | -22.7%*<br>+3.9% | NR |
| Gnant M. 2009 (ABCSG12) | Zoledronic Acid<br>No treatment | 4 mg IV q 6 mo | 3 yrs | 60 | 205<br>199 | 0%<br>1% | NR | NR | 76-77% | NR | NR | NR |
| Ellis GK. 2009 | Denosumab<br>Placebo | 60 mg sc q 6 mo | 2 yrs | 24 | 127<br>125 | 8%<br>10% | NR | -91%*<br>9% | NR | -29%*<br>-2% | NR | NR |
| Lester J. 2008 (ARIBON) | Ibandronate<br>Placebo | 150 mg oral q 28d | 2 yr | 24 | 25<br>25 | 8%<br>12% | -30.9% *<br>+39.5% | -26.3%*<br>+34.9% | 26.0%*<br>0% | NR | -22.8%*<br>+37.0% | NR |
| Saarto T. 1997 | Clodronate<br>Placebo | 1600 mg/d oral | 2 yrs | 24 | 44<br>49 | NR | NR | NR | 39%<br>29% | NR | NR | NR |
| Ahn JH. 2009 | Zoledronic acid<br>No treatment | 4 mg IV q 6 mo | 1 yr | 12 | 55<br>55 | NR | Lower*<br>s. no treat | Lower*<br>vs. no treat | NR | 72.7*<br>30.8 | Lower*<br>vs. no treat | N |

**Table 2A. Trials reporting BONE MINERAL DENSITY (BMD) for a bone-modifying agent versus placebo among patients at risk of CANCER-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration (Y)* | *Follow-up (M)* | *Patients (N)* | *Menopause (%)* | *Treat-ment* | *BMD, hip (% change)* | *BMD, spine (% change)* | *BMD, wrist (% change)* | *BMD, femoral neck (% change)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Greenspan SL (ReBBeCa) | Risedronate<br>Placebo | 35 mg/wk oral | 1 | 24 | 43<br>44 | 100<br>100 | AI<br>or CT | +0.9%*<br>-1.6% | +0.4%*<br>-1.2% | -1.7%<br>-2.1% | -0.0%*<br>-1.6% |
| McCloskey E. 2010 | Clodronate<br>Placebo | 1600 mg/d oral | 2 | 60 | 419<br>432 | 50<br>52 | AI<br>or CT | +0.52%*<br>-0.77% | +0.06%*<br>-1.87% | NR | -2.35%*<br>-4.05% |
| Aft R. 2010 | Zoledronic acid<br>No treatment | 4 mg IV q 3 wk | 1 | 24 | 60<br>59 | 48<br>44 | AI<br>or CT | +5.79*<br>-3.53 | +2.31*<br>-4.42 | +1.17*<br>-1.41 | NR |
| Hershman DL. 2010 | Zoledronic acid<br>Placebo | 4 mg IV q 6 mo | 1 | 24 | 50<br>53 | 0<br>0 | AI / CT | +0.8%<br>-2.6% | -0.6%<br>-6.3% | NR | +0.04%<br>-2.4% |

**Table 2B. Trials reporting BONE TURNOVER for a bone-modifying agent versus placebo among patients at risk of CANCER-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration* | *F/U (M)* | *Pts (N)* | *Fractures* | *l-telopept.* | *C-term. telo* | *T >-1* | *PINP* | *Bone ALP* | *SRE* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hershman DL. 2010 | Zoledronic acid<br>Placebo | 4 mg IV q 6 mo | 1 yr | 24 | 50<br>53 | NR | NR | No sig diff at 24 m | NR | NR | Not sig at 24 m | NR |
| Aft R. 2010 | Zoledronic Acid<br>No treatment | 4 mg IV q 3 wk | 1 yr | 24 | 60<br>59 | 0%<br>0% | -54.46%*<br>+31.49% | NR | NR | NR | -32.75%*<br>+31.90% | NR |
| McCloskey E. 2010 | Clodronate<br>Placebo | 1600 mg/d oral | 2 yrs | 60 | 419<br>432 | NR | No sig diff at 36 m | NR | NR | Not sig at 36 m | Not sig at 36 m | NR |
| Greenspan S (ReBBeCa) | Risedronate<br>Placebo | 35 mg/wk oral | 1 yr | 24 | 43<br>44 | 7.0%<br>4.5% | -6.5%*<br>+39.4% | NR<br>NR | NR<br>NR | +2.8%<br>+37.2% | NR | NR |
| Kristensen B. 2008 | Pamidronate<br>No treatment | 150 mg/d x 2 oral | 4 yrs | 48 | 460<br>493 | 7.2%<br>4.7% | NR | NR | NR | NR | Not sig at 60 m | NR |
| Hortobagyi GN. 1998 | Pamidronate<br>Placebo | 90 mg IV q 3-4 weeks | 2 yrs | 24 | 185<br>197 | 25% verteb<br>26% verteb | NR | NR | NR | NR | -29%*<br>+9% | 50%*<br>70% |

**Table 3. Trials reporting BMD and BONE TURNOVER comparing ONE AGENT vs. ANOTHER AGENT among patients at risk of CANCER-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration* | *Follow-up (M)* | *Patients (N)* | *N-telopeptide (% change)* | *C-terminal telo-peptide (%)* | *PINP (% change)* | *Bone ALP (% change)* | *SRE* |
|---|---|---|---|---|---|---|---|---|---|---|
| Stopeck A. 2009 | Zoledronic acid<br>Denosumab | 4 mg IV q 4 wks<br>120 mg sc | 12 mos | 34 | 2046 | NR | NR | NR | NR | HR **0.82** (0.71-0.95);*<br>30.7% ≥1 SRE<br>36.5% ≥1 SRE |
| Body JJ. 2008 | Denosumab<br>BP *(zol, pam, iba)* | 30/120/180 mg sc q4w<br>60/180 mg sc q12w<br>IV q4w, as per label | 6 mos | 7 | 127<br>85 | -75% (25 wk)<br>-71% (25 wk) | No sig diff at 36 mos | No sig diff at 36 mos | No sig diff at 36 mos | 12% ≥1 SRE<br>16% ≥1 SRE |
| Body JJ. 2007 | Ibandronate<br>Zoledronic acid | 50 mg/day<br>4 mg IV q 4 wks | 3 mos | 3 | 137<br>138 | NR<br>NR | -76%<br>-73% | -47%<br>-39% | -37%<br>-26% | NR<br>NR |
| Rosen LS. 2004 | Zoledronic acid<br>Pamidronate | 4 mg IV q 3-4 w<br>90 mg IV q 3-4 w | 24 mos | 25 | 372<br>140 | NR | NR | NR | NR | HR **0.8*** (vs. Pam)<br>46% ≥1 SRE<br>49% ≥1 SRE |

**Table 4. Trials reporting BMD and BONE TURNOVER comparing TIMING of bisphosphonates among patients at risk of TREATMENT-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration (Y)* | *Follow-up (M)* | *Patients (N)* | *Meno-pause (%)* | *AI (%)* | *BMD, hip (% change)* | *BMD, spine (% change)* | *Fractures (%)* | *N-telopep. (% change)* | *T-score (%)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brufsky AM. 2009 (Z-FAST) | - upfront<br>- delayed | 4 mg IV q 6 mo | 5 | 60 | 300<br>300 | 100<br>100 | 100<br>100 | +2.6%*<br>-4.1% | +6.2%*<br>-2.4% | 10.7%<br>12.4% | -15.1% *<br>+19.9% | 9% <-2; 27.9% >-1<br>.9% <-2; 8.6% >-1 |
| Eidtmann H. 2008 (ZO-FAST) | - upfront<br>- delayed§ | 4 mg IV q 6 mo | 5 | 36 | 532<br>533 | 3.6<br>83.1 | 100<br>100 | +5.41%*<br>(vs. delayed) | +9.29%*<br>(vs. delayed) | 4.6%<br>4.9% | 33% lower*<br>(vs. delayed) | 61.0% >-1<br>43.8% >-1 |
| Brufsky AM. 2008 (META Z/ZO-FAST) | - upfront<br>- delayed§ | 4 mg IV q 6 mo | 5 | 12 | 832<br>833 | 89.5<br>89.2 | 100<br>100 | +1.2%<br>-2.2% | +2.0%*<br>-3.1% | 2.2% (12 m)<br>2.1% (12 m) | -21.3% *<br>+21.7% | 1% <-1<br>17% <-1 |
| Llombarto A. 2009 (EZO-FAST) | - upfront<br>- delayed§ | 4 mg IV q 6 mo | 5 | 36 | 252<br>270 | 100<br>100 | 100<br>100 | NR | +9.6%*<br>(vs. delayed) | 2.0%<br>3.3% | NR | NR |
| Hines SL. 2009 (N03CC) | - upfront<br>- delayed§ | 4 mg IV q 6 mo | 5 | 24 | 197<br>198 | 100<br>100 | 100<br>100 | +1.22%*<br>-3.34% | +4.94%*<br>-2.28% | NR | NR | NR |
| Xi-Chun H. | - weekly<br>- 1 dose | 1 mg/wk IV q4w<br>4 mg IV (1 dose) | n/a | 1 | 30<br>30 | NR | NR | NR | NR | NR | Reduced *<br>(vs. 1 dose) | NR |

**Table 5. Trials reporting RECURRENCE or SURVIVAL comparing TIMING of bisphosphonates among patients at risk of TREATMENT-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration (Y)* | *F/U (M)* | *Patients (N)* | *DFS (%)* | *RFS (%)* | *OS (%)* | *Recurrence (%)* | *Bone Mets (%)* |
|---|---|---|---|---|---|---|---|---|---|---|
| Llombarto A. '09 (ZO-FAST) | - upfront<br>- delayed§ | 4 mg IV q 6 mo | 5 | 36 | 532<br>533 | 95.1%<br>91.9% | NR | 99.2%<br>99.1% | 6.9%<br>4.2% | 3.8%<br>3.0% |
| Brufsky AM. '09 (Z-FAST) | - upfront<br>- delayed | 4 mg IV q 6 mo | 5 | 60 | 300<br>300 | 95.0%<br>92.4% | NR | 93.0%<br>91.2% | 3.0%<br>5.3% | NR |
| Brufsky AM. '08 (Z/ZO-FAST) | - upfront<br>- delayed§ | 4 mg IV q 6 mo | 5 | 12 | 832<br>833 | 98.9%*<br>97.7% | NR | 99.5%<br>99.4% | 0.84%*<br>1.9% | NR |

**Table 6. Trials reporting RECURRENCE or SURVIVAL with bisphosphonates among patients at risk of CANCER-RELATED BONE LOSS.**

| *Author (Trial)* | *Intervention* | *Administration* | *Duration (Y)* | *F/U (M)* | *Patients (N)* | *DFS (%)* | *RFS (%)* | *OS (%)* | *Recurrence (%)* | *Bone Mets (%)* |
|---|---|---|---|---|---|---|---|---|---|---|
| Coleman RE 2011 | Adj zoledronic<br>No ZA | 4 mg x 6 q 3-4w then q3-6m | 5 | 59 | 3360<br>total | 77%<br>77% | NR<br>NR | 85.4%<br>83.1% | NR<br>NR | NR<br>NR |
| Body JJ. 2008 | Denosumab<br><br>*zol, pam, or iba* | 30/120/180 q4w<br>60/180 mg q12w<br>as per label | 0.5 | 7 | 42/ 42/ 43<br>42/ 43<br>42 | NR | NR | 85%<br><br>81% | NR | NR |
| Kristensen B. 2008 | Pamidronate<br>No treatment | 150 mg/d x 2 oral | 4 | 48 | 460<br>493 | NR | NR | 45%<br>46% | NR | 20.7%<br>18.4% |
| Diel IJ. 2008 | Clodronate<br>No treatment | 1600 mg/d oral | 2 | 103 | 157<br>145 | No difference (vs. no treat) | No diff (vs. no treat) | 79.6%<br>59.3% | 38.9% (distant)<br>39.3% (distant) | 23.6%<br>26.2% |
| Saarto T. 2008 | Clodronate<br>Placebo | 1600 mg/d oral | 3 | 120 | 139<br>143 | 45%*<br>58% | NR | 54%<br>62% | 29% (local)<br>22% (local) | 32%<br>29% |
| Kohno N. 2005 | Zoledronic acid<br>Placebo | 4 mg IV (15-min) q 4 weeks | 1 yr | 12 | 114<br>114 | 25.4%*<br>38.9% | NR | NR | NR | NR |
| Tripathy D. 2004 | Ibandronate<br>Placebo (P) | 20 or 50 mg/d oral | 2 yrs | 24 | 148 / 144<br>143 | No diff vs. placebo | NR | -39%*<br>+47% | NR | NR |
| Body JJ. 2003 | Ibandronate<br>Placebo (P) | 2 or 6 mg q 3-4 w<br>2 mg q 3-4 w | 2 yrs | 24 | 154 / 154<br>158 | -11%* vs. placebo | NR | NR | NR | NR |
| Lipton A. 2000 | Pamidronate<br>Placebo | 90 mg IV q 3-4 w for 24 cycles | 2 yrs | 24 | 367<br>384 | 40%*<br>52% | NR | NR | NR | NR |
| Mardiak J. 2000 (abstract) | Clodronate<br>Placebo | 1600 mg/d oral | 2 | 60 | 37<br>36 | NR | NR | 41%<br>39% | 48% (non-bone)<br>48% (non-bone) | 30%<br>23% |
| Powles T. 2002 | Clodronate<br>Placebo | 1600 mg/d oral | 2 | 67 | 530<br>539 | NR | NR | 81.5%*<br>76.1% | 26.2%<br>26.9% | 9.6%*<br>13.5% |
| Conte PF. 1996 | Pamidronate<br>No treatment | 45 mg IV q 3 wks | 1 | 12 | 143<br>152 | NR | NR | 19.7 mo<br>21.1 mo | NR | 62.1%<br>63.9% |
| Theriault RL. 1999 | Pamidronate<br>Placebo | 90 mg IV q 4 w for 24 cycles | 2 | 24 | 182<br>189 | NR | NR | 81%<br>89% | 30%<br>24% | NR |
| Kristensen B. 1999 | Clodronate<br>No treatment | 800 mg/d oral | 2 yrs | 24 | 49<br>51 | 6.1%*<br>25.5% | NR | NR | NR | NR |
| Theriault RL. 1999 | Pamidronate<br>Placebo | 90 mg IV q 4 w for 24 cycles | 2 yrs | 24 | 182<br>189 | 45%<br>55% | NR | NR | NR | NR |