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Title; Adjuvant zoledronic acid reduces fractures in breast cancer patients; an AZURE (BIG 01/04) study.

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Abstract

The fracture impact of adjuvant bisphosphonates in breast cancer is not defined with most trials reporting changes in bone mineral density as a surrogate. The AZURE trial (ISRCTN79831382) evaluated the impact of adjuvant zoledronic acid (ZOL) on fractures.

The AZURE trial is an academic, multi-centre, randomised phase III study evaluating the addition of ZOL 4mg to standard therapy (neo/adjuvant chemotherapy and/or endocrine therapy) for 5 years (administered by intravenous (iv) infusion every 3-4 weeks for 6 doses, then 3 monthly x 8 and 6 monthly x 5) in patients with stage II/III early breast cancer. Fracture data collected as part of skeletal related adverse event reporting were analysed after a median of 84.2 months of follow up and 966 disease free survival (DFS) events. We assessed number of fractures, time to first fracture and the incidence of fractures before and after disease recurrence.

244 patients reported ≥1 fracture, 140 (8.3%) in the control arm (171 fractures) and 104 (6.2%) in the ZOL arm (120 fractures). Of the 291 fractures reported, 207 fractures occurred in the absence of recurrence (Control 111, ZOL 96), 80 after recurrence (Control 59, ZOL 21). The 5-year fracture rate was reduced from 5.9% (95%CI 4.8, 7.1%) (control) to 3.8% (95%CI 2.9, 4.7%) with ZOL. ZOL significantly increased time to first fracture (HR 0.69, 95% CI 0.53-0.90 p=0.0053) but the majority of fracture prevention benefit occurred after a DFS event (HR 0.3; 95%CI 0.17, 0.53 $P<0.001$). Fracture benefits from ZOL were similar across menopausal sub-groups.

In conclusion, adjuvant zoledronic acid reduced the risk of clinical fractures, the majority of this protection occurred after disease recurrence.

Key words; adjuvant, zoledronic acid, fractures, breast cancer.

Introduction

Adjuvant chemotherapy and endocrine treatments are an integral part of the multi-modality management of early breast cancer used to reduce the risk of disease recurrence and mortality. However, these therapies result in bone loss, either due to the direct effect on the balance of bone formation by osteoblasts and bone resorption by osteoclasts, or due to indirect effects of lowering systemic oestrogen (ovarian failure/suppression in premenopausal patients and aromatase inhibitors (AIs) in postmenopausal women)[1,2]. A breast cancer diagnosis *per se* is associated with an increased risk of fracture in the absence of metastatic disease [3,4] and standard risk estimation scores (i.e. FRAX) underestimate fracture risk [5]. Fractures impair quality of life, increase health care costs and decrease survival [6].

Because of the adverse impact of treatments on bone health, breast cancer patients may require intensive bone protective management. Postmenopasual women have a natural yearly loss in bone mineral density (BMD) at the lumbar spine of 1%/year; rising to 2%/year in breast cancer patients receiving AIs and up to 7%/year in premenopausal patients with treatment induced ovarian failure [6]. Bisphosphonates can prevent treatment related bone loss, with most data available for zoledronic acid (ZOL) which prevents both the bone loss associated with AIs and with ovarian failure/suppression [7,8] . The majority of adjuvant bisphosphonate studies, as bone protective agents, have focused on changes in BMD as the primary endpoint and were not designed to reliably assess treatment effects on fracture incidence [9-14].

The AZURE study is an academic, multi-centre, international phase III trial that randomized patients with early breast cancer to standard adjuvant therapy (chemotherapy and/or endocrine therapy) alone or with the addition of an intravenous infusion of ZOL 4mg for 5 years (administered every 3-4 weeks for 6 doses, then 3 monthly x 8 and 6 monthly x 5). The efficacy data have been published previously [15,16] with disease free survival (DFS) events showing that, despite a reduction in the risk of developing bone metastases, there was no effect on overall breast cancer recurrence. However, preplanned subgroup analyses identified benefit in women who were in established menopause at the time of study entry (n=1041, adjusted HR 0.77;

95%CI 0.63, 0.96), an observation which has been confirmed by the Early Breast Cancer Clinical Trials Collaborative Group (EBCTCG) meta-analysis of >18,000 women included in randomized trials of adjuvant bisphosphonates.[17]

The AZURE study also collected data on fractures as part of skeletal related event reporting by treating clinicians and represents one of the largest data sets for evaluation of fracture incidence in patients treated +/- ZOL during adjuvant therapy. In this study we present the data on fractures, as a pre-planned secondary end point analysis, to assess the effects of ZOL on fractures pre- and post disease recurrence and the differential effect according to menopausal status at baseline.

Patients and methods

Eligibility criteria have been reported previously [15]. To summarise, eligible patients had; histologically confirmed invasive breast cancer, pathologically involved axillary lymph node metastasis or a T3/T4 primary tumour, complete resection of the primary tumour or planned resection if receiving neoadjuvant chemotherapy, aged ≥18 years, Karnofsky performance status index ≥80, not pregnant or breast-feeding. Patients were ineligible if there was clinical/imaging evidence of distant metastases prior to study entry, current, recent (previous year) or intended use of bisphosphonates for pre-existing bone disease.

Between September 2003 and February 2006, 3360 patients were randomized 1:1 using a computer generated system which included the following minimization criteria; number of involved lymph nodes, clinical tumour stage, oestrogen receptor status, clinical menopausal status, type and timing of systemic therapy, study centre and statin use.

Patients received standard adjuvant therapy and locoregional treatments according to institutional protocols +/- intravenous ZOL, 4mg every 3 to 4 weeks for 6 cycles and then every 3 months for 8 doses, followed by 5 cycles on a 6-month schedule for a total of 5 years[15]. Once distant recurrence was identified trial medication was stopped and

patients were treated as per local site protocol. Ethical approval was obtained for all participating centres and all patients gave written informed consent before enrolment.

Patient evaluation

Fractures were reported as part of trial follow-up visits, occurring 3-4 weekly for the first 6 months, 3-monthly to 2.5 years, 6-monthly to 5 years and annually to 10 years. Fractures were reported on the case report form (CRF) as a specific skeletal related event and recorded as present or not, site(s) involved, date of onset and cause. Fractures were recorded in relation to DFS events. If a fracture occurred prior to disease recurrence the causality of the fracture was recorded as traumatic or non-traumatic including osteoporosis. Fractures that occurred after a DFS event were recorded as traumatic or non-traumatic including pathological fracture

Statistical methods

Statistical analysis was performed on the 'final analysis' data[16]. Data lock occurred after a median of 84.2 (IQR 71-92) months of follow up and 966 disease-free survival events. All analyses were performed on the intention-to-treat population using SAS version 9.2 or 9.4.

Cumulative incidence function curves were used to investigate time to first fracture pre- and post-DFS event, to account for death as a competing risk. Cox's proportional hazards model was used to compare differences between the two treatment arms, adjusting for minimization factors. An interaction between menopausal status and treatment was included in the model when assessing differences by menopausal status.

Patients with any missing fracture dates were censored at the last date they were known to be alive and without any fractures in the main analysis (n=19). A sensitivity analysis was performed to include these patients as having had an event (taken to be the mid-point between follow-up date at which the fracture was reported and the last date the patient was known to be without any fractures).

Results

Patient characteristics

3359 patients were eligible for inclusion in this analysis (see figure 1). Patient demographics have been published previously[15] and those relevant for this analysis are summarised in table 1. Additional risk factors for fracture including smoking, alcohol, family history of osteoporosis and previous fragility fracture were not routinely recorded. Baseline bone density measurements were not routinely performed.

Fracture incidence

244 patients experienced one or more fractures on study, 140 (8.3%) in the control arm (171 fractures) and 104 (6.2%) in the ZOL arm (120 fractures). Of the 291 fractures reported, 171 fractures were due to trauma; of these 93 (54.4%) were in control patients and 78 (45.6%) in ZOL patients. 111 were non-traumatic fractures; of these 75 (67.6%) were in the control arm and 36 (32.4%) in the ZOL arm (causality was not specified for 9 fractures). The 5 year fracture rate for patients receiving ZOL was significantly reduced to 3.8% (95%CI 2.9, 4.7%) compared with 5.9% in the control arm (95%CI 4.8, 7.0%); an overall difference in the proportion of patients experiencing a fracture within 5 years of -2.2% (95%CI -3.9, -0.4%). In addition, time to first fracture was significantly increased in the ZOL arm compared to control (HR 0.69, 95%CI 0.53, 0.90 [*P*=0.0053]) (see figure 2A). In the multivariate analysis (adjusted for minimization factors) only treatment allocation was significantly associated with time to first fracture (see figure 3). This interpretation was unchanged when missing fracture data were included as described in the sensitivity analysis (HR 0.72, 95%CI 0.56, 0.93 [*P*=0.012]). Fracture incidence was reduced in both oestrogen (ER) positive and negative disease (ER positive; control 9.16%, ZOL 6.71%, ER negative; control 6.36%, ZOL 4.35%) suggesting benefit is gained from ZOL irrespective of the use of endocrine therapies.

Fractures and disease recurrence

Fractures were recorded in relation to DFS events. 207 fractures occurred before or in the absence of a DFS event (111 (54%) in the control arm and 96 (46%) in the ZOL arm)

(see figure 2B). ZOL reduced fractures compared to control at recognised sites of major osteoporotic fractures including the femur (inclusive of neck of femur) (0.11% vs 0.29%), wrist (0.59% vs 1.25%) and spine (0.23% vs 0.59%) (see table 2).

80 fractures occurred after a DFS event (59 (73.8%) in the control arm and 21 (26.3%) in the ZOL arm (relationship to recurrence was unknown in 4) (see figure 2C),. Adjuvant ZOL reduced fractures compared to control after a DFS event in the femur (inclusive of neck of femur) (1.27% vs 2.03%) and spine (0.85% vs 3.04%) in addition to other sites such as ribs and pelvis (see table 2). Of the 80 fractures that occurred after a DFS event the majority occurred in patients who experienced a skeletal recurrence (n=60); 45 (75%) were in the control arm and 15 (25%) were in the ZOL arm. The majority of fracture prevention benefit from adjuvant ZOL appeared to occur after a disease recurrence event (HR 0.30, 95% CI 0.17, 0.53; *P*<0.0001). The 2 year fracture rate for patients in the ZOL arm following a DFS event was substantially reduced from 9.8% (95%CI 7.1, 12.6%) in the control arm to 2.8% (95%CI 1.2, 4.4%), with an absolute difference in the proportion of patients in each treatment group experiencing a fracture within 2 years post-disease recurrence of 6.1% (95%CI 9.3, 3.0%).

Fractures and menopausal status at study entry

166 patients classed as pre-, peri or unknown menopausal status at study entry experienced a fracture, 98 (4.23%) in the control arm and 68 (2.93%) in the ZOL arm. The most common sites for fracture in this menopausal sub-group within the control arm were the spine (0.82%), ribs (1.08%) and wrist (0.73%) while, in the ZOL arm, the most common fracture sites were ribs (0.6%), arm (0.52%) and foot (0.43%). 78 patients defined as >5 years postmenopausal at study entry experienced a fracture, 42 (4.03%) in the control arm and 36 (3.46%) in the ZOL arm. The most common sites for fracture in this menopausal sub-group in the control arm were the femur (0.96%), leg (below knee) (1.05%) and arm (0.77%) while, in the ZOL arm, the most common fracture sites were the arm (0.77%), foot (0.77%) and wrist (0.58%). The 5 year fracture rate for ZOL patients was reduced in both menopausal groups compared to the control arm (see figure 4A), however, the greatest reductions in fractures with ZOL were seen in the 2 years following a DFS event for both menopausal groups (see figure 4B).

Menopausal status did not significantly influence the benefit gained in fracture prevention with ZOL, with similar reductions in the overall population and in post-DFS event fracture rates across all menopausal groups (relative difference in the HRs for treatment (ZOL vs. control) between menopausal groups; overall HR=0.76, 95%CI 0.427, 1.33; *P*=0.33; post DFS 1.72, 95%CI 0.432, 6.855; *P*=0.43) (see table 3).

Skeletal Toxicity

26 cases of osteonecrosis of the jaw (ONJ) were confirmed in patients treated with ZOL giving an ONJ rate of 1.7% (95%CI 1.1-2.4). The majority of cases occurred whilst on or within 6 months of stopping study medication. No cases of ONJ were confirmed in the control arm. No atypical femoral fractures were recorded.

Discussion

These results from the AZURE study show that in a mixed menopausal population, adjuvant ZOL reduced the incidence and rate of fractures. Compared to standard adjuvant treatment, both fracture incidence and time to first fracture were significantly improved with ZOL, and the 5-year fracture rate in patients receiving ZOL reduced to a rate that is similar to that reported in non-breast cancer patients (3.97% 95%CI 3.94, 3.99) [18]. The majority of the benefit in fracture prevention was seen after disease recurrence in patients who developed metastases, especially at bony sites. At disease recurrence trial medication was stopped and patients received treatment as per local site protocol, including, where appropriate, bone targeted treatments, suggesting the difference in fracture rates after disease recurrence is due to improvements in the structural integrity of the skeleton by ZOL prior to disease recurrence.

The limitations of our study include the possible under ascertainment of fractures, considering that they were reported as part of skeletal-related adverse event (AE) reporting and not actively monitored with serial imaging. However this limitation will have likely affected both treatment groups similarly and would not be expected to

change the overall conclusions. Symptomatic fractures that result in AE reporting are also likely to be of greater clinical significance than those identified on serial imaging.

Adjuvant ZOL has been shown to reduce BMD loss in premenopausal women treated with ovarian suppression and tamoxifen/ anastrazole [7], premenopausal women with ovarian failure due to chemotherapy [19,20] and postmenopausal women receiving AIs [13,21,22]. In these bone protection studies, the majority of patients received a 6 monthly regimen of ZOL. Fracture rates were not reported in most of these studies but, preservation of BMD has been shown to correlate with a reduced fracture risk [23,24]. Our data suggests that whilst adjuvant ZOL does reduce fracture incidence prior to disease recurrence, this effect is perhaps more modest that was assumed from the BMD studies. Bone health guidelines during cancer therapy commonly recommend assessment of fracture risk and treatment with bisphosphonates if baseline BMD T score is <2.0 or if two or more clinical risk factors for fracture are present [14]. Many fractures occur in patients with normal BMD and thus both patient monitoring and treatment decisions should consider all risk factors for fracture.

Recently the ABSCG-18 study has shown that the addition of the alternative osteoclast inhibitor, denosumab 60mg every 6 months, in postmenopausal women on AIs, halves fracture rates irrespective of baseline T score[25] . This study provides the best evidence to date for fracture prevention in early breast cancer. The study also supports the recommendation that selecting patients for treatment with osteoclast inhibitors on the basis of baseline BMD or loss of BMD over time may undertreat some patients at risk of fracture on adjuvant systemic therapy. The rate of fractures in the placebo treated patients within ABCSG-18 was higher than that seen in our study (9.6% 95%CI 8.0, 11.2 at 36 months), which is unsurprising considering that AZURE recruited a lower risk population by including both pre and postmenopausal women and included those with oestrogen receptor positive or negative tumours, thereby resulting in limited use of AIs.

In our study the predominant fracture prevention benefit of adjuvant ZOL after disease recurrence, when the majority of patients will be established on bone targeted agents for skeletal recurrence irrespective of adjuvant treatment, is of interest. Zoledronic acid

is known to have long term effects on bone metabolism years after treatment has ceased [26] which may improve the resilience of bone in the presence of metastatic disease. In ABCSG-18 the effects of denosumab on fractures occurring after disease recurrence were not specifically reported, although a sensitivity analysis with patients censored at the time of disease recurrence did not change the overall results, suggesting that the predominant benefit from adjuvant denosumab is on the prevention of adjuvant treatment related fractures. Denosumab's short half-life in bone compared with a bisphosphonate may limit effects on skeletal morbidity after disease recurrence. This shorter duration of action of denosumab is reflected by reports of increased fracture rates on cessation of the drug in the osteoporosis setting [27].

The 1.7% incidence of ONJ in AZURE patients receiving ZOL needs to be considered. The ONJ rate in AZURE is higher than was identified in studies of ZOL administered every six months (ABCSG-12, ZOFAST, Z-FAST and EZO-FAST) in which only 2 cases of ONJ have been reported in over 4000 patients [28]. This probably reflects the more intense schedule ZOL used in the first 6 months of the AZURE study. Of note, there were no cases of ONJ identified in the ABCSG-18 study [25] and therefore risk vs benefit of treatment favours denosumab in postmenopausal women for fracture prevention alone, whereas in higher risk patients in whom disease recurrence prevention is a priority, adjuvant BPs can reduce breast cancer mortality [17] in addition to reducing fracture risk, which offsets the small risk of ONJ.

The recently published large meta-analysis of randomised trials of adjuvant bisphosphonates demonstrated the reduction in breast cancer recurrence rates and breast cancer mortality in postmenopausal women [17]. However, whether denosumab also has this effect is not yet known. In the ABSCG-18 study, Gnant and colleagues reported fewer DFS events in patients treated with denosumab (n=167) compared to placebo (n=203), equivalent to an 18% reduced risk of recurrence at a median follow up of 4 years[29]. However, the study was unblinded and patients offered active treatment from 2016, so reliable longer follow-up information/survival data from this trial may not become available. The role of adjuvant denosumab on disease recurrence is being formally evaluated in the D-CARE study (NCT01077154) which, like AZURE, randomised a

broad range of patients at high risk of recurrence; results from this study will be available in 2018. Until then, the role of adjuvant denosumab should be limited to fracture prevention in women at low risk for breast cancer recurrence and, as suggested by clinical guidelines [30] should not be prioritized over the use of an adjuvant bisphosphonate.

Adjuvant bisphosphonates have now become the standard of care for many postmenopausal women to reduce bone recurrence and improve breast cancer survival. Our study, in addition to identifying the disease recurrence benefits of adjuvant ZOL in postmenopausal women with early breast cancer, has shown a modest added benefit of a reduction in fracture rates, further strengthening the role of bisphosphonates in the adjuvant setting.

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Conflict of Interest Statement

C Wilson declares speaker fees from Amgen; R. Coleman reports grants from Bayer, grants from Amgen and personal fees from Eisai and Astra Zeneca outside the submitted work; R Bell reports grants from The Cancer Council Victoria (Australia) during the conduct of the study; JB reports grants from Amgen and honoraria from Amgen, Novarits, Bayer and Pfizer; DC, HM, DD, SH have no conflicts to declare.

References

1. Coleman, R.E., E. Rathbone, and J.E. Brown, Management of cancer treatment-induced bone loss. Nature reviews. Rheumatology 9(6): p. 365-74, 2013

2. Wilson, C. and R.E. Coleman, Adjuvant therapy with bone-targeted agents. Current opinion in supportive and palliative care,5(3): p. 241-50, 2011

3. Kanis JA, McCloskey EV, Polwes T et al, A high Incidence of vertebral fracture in women with breast cancer Br J Cancer 79:1179-118, 1999

4. Chen Z, Maricic M, Bassford TL et al. Fracture risk among breast cancer survivors:results from the Women's Health Initiative Observational study. Arch Intern Med;165:552-558, 2005

5. Hadji P, Coleman R, Wilson C et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol Mar;27(3):379-90. doi: 10.1093/annonc/mdv617, 2015.

6. Body JJ. Increased fracture rate in women with breast cancer: a review of the hidden risk. BMC Cancer 11: 384,2011

7. 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 ABCSG-12 bone-mineral density substudy. Lancet Oncol 9:840-9,2008.

8. Hershman DL, McMahon DJ, Crew KD, et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 26:4739-45, 2008.

9. 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 14:6336-42,2008.

10. Saarto T, Blomqvist C, Valimaki M et al. Chemical castration induced by adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. J Clin Oncol 15:1341-7,1997.

11. Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol 28:967-75,2010.

12. 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 25:829-36,2007.

13. 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 24:398-405,2013.

14. Coleman R, Body JJ, Aapro M,et al. Bone health in cancer patients: ESMO Clinical Practice Guidelinesdagger. Ann Oncol 25 Suppl 3:iii124-iii37,2014.

15 Coleman RE, Marshall H, Cameron D et al. Breast Cancer adjuvant therapy with zoledronic acid. New England Journal of Medicine;365:1396-1405, 2011.

16. Coleman RE, Cameron D, Dodwell D et al. Adjuvant zoledronic acid in patients with early breast cancer:final efficacy anlysis of the AZURE (IG 01/04) randomised open-label phase 3 trial. Lancet Oncol;15:997-1006, 2014.

17 Early Breast Cancer Trialists Cooperative Group. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomized trials. Lancet386(10001):1353-1361, 2015.

18. Colzani E, Clements M, Czene K et al. (2016). Risk of hospitalisation and death due to bone fractures after breast cancer: a registry-based cohort study. British Journal of Cancer 115:1400–1407. doi:10.1038/bjc, 2016.

19. 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 47:683-9, 2011.

20. Kim JE, Ahn JH, Jung KH, et al. Zoledronic acid prevents bone loss in premenopausal women with early breast cancer undergoing adjuvant chemotherapy: a phase III trial of the Korean Cancer Study Group (KCSG-BR06-01). Breast Cancer Res Treat 125:99-106, 2011.

21. 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 25:829-36,2007.

22. Llombart A, Frassoldati A, Paija O, et al. Immediate Administration of Zoledronic Acid Reduces Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women With

Early Breast Cancer: 12-month analysis of the E-ZO-FAST trial. Clin Breast Cancer 12:40-8, 2012.

23. Coleman R, Body JJ, Aapro M et al. Bone health in cancer patients: ESMO Clinical Practice Guidelinesdagger. Ann Oncol 25 Suppl 3:iii124-iii37, 2014.

24. Sestak I, Singh S, Eastell R. 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 Oncol15(13):1460-8. doi: 10.1016/S1470-2045(14)71035-6, 2014.

25. Gnant M, Pfeiler G, Dubsky PC et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet ;386:433-443,2016

26. Brown JE, Ellis SP, Coleman RE et al .Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. Clin Cancer Res 15;13(18 Pt 1):5406-10, 2007

27. Aubry-Rozier B, Gonzalez-Rodriguea E, Stoll D et al. Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports. Osteoporosis International 5:1923–1925, 2016.

28. Coleman R, Woodward E, Thorpe H. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01–04) for women with stage II/III breast cancer . Breast Cancer Res and Treat:127;429-438, 2011

29. Gnant M, Pfeiler G, Dubsky PC, et al. The impact of adjuvant denosumab on disease-free survival: results from 3425 postmenopausal patients of the ABCSG-18 trial. Presented at: 2015 San Antonio Breast Cancer Symposium; San Antonio, TX; December 8-12, (abstr S2-02), 2015

30.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(18): 2062-2081.

31. Body **J.** Increased fracture rate in women with breast cancer: a review of the hidden risk. BMC Cancer. 2011; 11: 384.

Figure legends

Figure 1. Consort diagram trial profile.

Note that more than 1 reason was given for some patients not receiving allocated zoledronic acid.

Figure 2 Cumulative incidence function curve of time to first fracture by randomized treatment, Overall (A) , before disease recurrence (B) and after disease recurrence (C). (In A, 19 patients had missing fracture dates and in B 1 patient in the ZOL arm had a missing fracture date. These patients were censored at the last date known to be alive without any fractures).

Figure 3: Forest plot based on hazard ratios for factors included in the multivariate analysis of time to first fracture. Error bars are 95%CIs

Figure 4. Interactions between menopausal status, treatment allocation and frequency of clinical fractures

A. Overall 5 year fracture rates in patients treated with standard therapy (control) and standard therapy plus zoledronic acid (ZOL) according to menopausal status. Error bars are 95% CIs. Hazard ratios for time to first fracture according to menopausal status are 0.45-0.88 for pre, peri, unknown menopausal group and 0.52-1.33 for >5 years postmenopausal.

B 2 year fracture rates post DFS event in patients treated with standard therapy alone (control) and standard therapy plus zoledronic acid (ZOL) according to menopausal status. Error bars are 95% CIs. Hazard ratios for time to first fracture post DFS event according to menopausal status are 0.21-0.71 for pre, peri, unknown menopausal group and 0.06-0.75 for >5 years postmenopausal.