Original Study

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

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Abstract

Aromatase inhibitors (AIs), an increasingly common adjuvant treatment option for postmenopausal women with hormone receptor-positive early breast cancer, are associated with bone loss that can impair patient quality of life. This study (E-ZO-FAST; Clinical Trials Identifier: NCT00171314) demonstrates that initiation of zoledronic acid therapy concurrent with adjuvant AI treatment improved skeletal health compared with zoledronic acid therapy initiated after deterioration of bone health.

Background: Letrozole is a proven and effective adjuvant therapy in postmenopausal women with hormone receptor–positive (HR^+) early breast cancer (EBC). As with other aromatase inhibitors (AIs), long-term letrozole administration is associated with decreased bone mineral density (BMD) and increased fracture risk. This study compared potential bone-protecting effects of immediate vs. delayed administration of zoledronic acid (ZOL) in patients with EBC receiving adjuvant letrozole. **Patients and Methods:** Patients with HR^+ EBC in whom adjuvant letrozole treatment was initiated (2.5 mg/day for 5 years) were randomized to immediate ZOL treatment (immediate ZOL) or delayed ZOL treatment (delayed ZOL) (both at 4 mg every 6 months). Patients in the delayed ZOL group received ZOL only for a BMD T-score that decreased to < -2.0 (lumbar spine [LS] or total hip [TH]) or for fracture. The primary endpoint was percentage change in the LS BMD at month 12. Patients were stratified by established or recent postmenopausal status, baseline T-scores, and adjuvant chemotherapy history. **Results:** At 12 months, the LS BMD increased in the immediate ZOL group (+2.72%) but decreased in the delayed ZOL group (–2.71%); the absolute difference between groups was significant (5.43%; $P < .0001$). Across all subgroups, patients receiving immediate ZOL had significantly increased LS and TH BMD vs. those who received delayed ZOL ($P < .0001$). Differences in fracture incidence or disease recurrence could not be ascertained because of early data cutoff and low incidence of events. Adverse events were generally mild, transient, and consistent with the known safety profiles of both agents. **Conclusion:** Immediate ZOL administration effectively prevented BMD loss and increased BMD in postmenopausal women with HR^+ EBC receiving adjuvant letrozole, regardless of BMD status at baseline.

Clinical Breast Cancer, Vol. 12, No. 1, 40-8

Keywords: Aromatase inhibitor, Bone mineral density, Early breast cancer, Letrozole, Postmenopausal, Zoledronic acid

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Submitted: Apr 21, 2011; Revised: Aug 5, 2011; Accepted: Aug 17, 2011

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1526-8209/$ - see frontmatter
doi: 10.1016/j.clbc.2011.08.002

Introduction

Aromatase inhibitors (AIs) are widely used for the adjuvant treatment of postmenopausal women with hormone receptor–positive (HR^+) early breast cancer (EBC) because these agents are highly effective at lowering estrogen levels.[1–5] However several large controlled studies have reported that adjuvant AI therapy is associated with a significantly higher fracture risk (approximately 2%-4%; $P \leq .02$ for all) compared with tamoxifen.[6–10]

Current European Society for Medical Oncology (ESMO) guidelines advocate managing AI-associated bone loss (AIBL) based on dual-energy x-ray absorptiometry (DEXA) bone mineral density (BMD) assessments and recommend using bisphosphonate (BP) therapy to allow early treatment of osteoporosis in patients treated with AIs.[5] Although it has become increasingly evident that BMD is only 1 of several risk factors for fragility fractures,[11] current guidelines do not take these into consideration. Recently, in the bone substudy from the ABCSG-12 trial (Austrian Breast and Colorectal Cancer Study Group–Trial 12) in premenopausal estrogen receptor-positive patients with breast cancer (BC), women receiving a luteinizing hormone–releasing hormone analogue concurrently with an AI (anastrozole) had a higher rate of bone loss compared with women who received tamoxifen.[12] Thus complete estrogen blockade as a result of treatment or postmenopausal status may predispose women to AIBL and increase the level of AIBL. Moreover, fragility fractures can occur in women with BMD T-scores > -2.0.[13] For example, the relative risk of fracture was 1.6-1.8 in patients with T-scores of –1.0 to > –2.0 compared with 2.6 in patients with T-scores of ≤ –2.0.[14] A decrease in BMD T-score to ≤ -1.0 in postmenopausal women as assessed by any current BMD assessment methodology at any site is associated with increased fracture risk.[14,15] Indeed it has been shown that fracture risk increases 1.5- to approximately 2-fold for every 1 standard deviation (the unit of the T-score) of BMD below normal.[14]

Based on the fact that maximal BMD loss at both the lumbar spine (LS) and trochanter typically occurs within the first 12 months after initiating endocrine therapy,[12] it is likely that early initiation of bone-conserving therapy might provide greater benefit. In the bone substudy from the ABCSG-12 trial in 404 premenopausal patients with BC, concomitant zoledronic acid (ZOL) (4 mg every 6 months) and 3 years of goserelin plus tamoxifen or anastrozole therapy significantly reduced bone loss at the 3-year follow-up and maintained BMD at the 2-year posttreatment follow-up level vs. endocrine therapy alone.[16] The 3 large randomized multicenter companion Zometa-Femara Adjuvant Synergy Trials—Z-FAST (N = 602 patients),[17] ZO-FAST (N = 1065 patients),[18] and the present E-ZO-FAST (N = 527 patients)—are similarly designed trials that compare the effects of immediate (initiated simultaneously with adjuvant treatment) vs. delayed (initiated only when a patient's BMD T-score decreased to < –2.0 at either the LS or total hip [TH], or the patient experienced a nontraumatic fracture) treatment with ZOL (both at 4 mg every 6 months) for preventing AIBL in postmenopausal women with early-stage BC. In all these studies, patients were stratified by BMD T-score and other risk factors and were scheduled to receive adjuvant letrozole for 5 years. Data from the Z-FAST[19] and ZO-FAST[20] studies, conducted primarily in North America and Europe, respectively, clearly demonstrated that early initiation of ZOL treatment improves clinical benefit in terms of prevention of AIBL compared with delayed ZOL treatment in the respective study populations. However these studies were conducted in relatively homogeneous populations, and validation of bone loss and preservation patterns in a global population is needed. The current study sought to extend these results to a patient population recruited across a broader geographic region that included Europe, Latin America, Africa, Asia, and the Middle East. This report presents results for the 12-month primary analysis of E-ZO-FAST.

Patients and Methods

Patients and Interventions

Patients were enrolled from 66 centers in Europe, Latin America, Africa, and the Middle East. Eligible patients were postmenopausal or recently menopausal from ovarian-ablative treatments and had resected stage I to stage IIIa HR^+ EBC, no clinical or radiologic evidence of recurrent or metastatic disease, baseline Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, and LS and TH BMD T-scores ≥ –2.0. Patients who discontinued hormone replacement therapy or oral BPs at least 3 weeks before study entry were eligible. Patients were excluded if they had distant metastases, existing LS or TH fracture, a history of fragility fractures, renal dysfunction, other malignancies, or diseases known to affect bone metabolism.

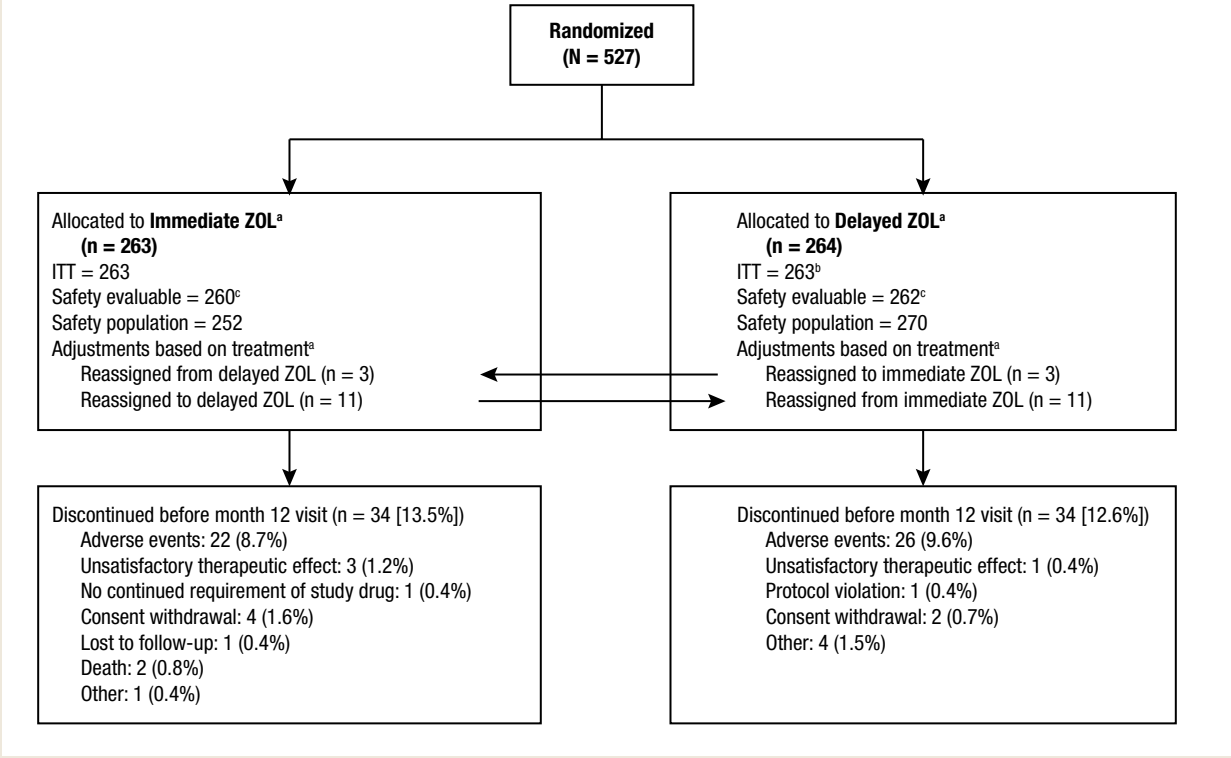
Study Design

This open-label randomized multicenter study (Figure 1) evaluated the effects of immediate or delayed treatment with ZOL 4 mg (dose modified based on renal function)[21] by 15-minute intravenous infusion every 6 months in postmenopausal women receiving adjuvant letrozole 2.5 mg daily for 5 years or until disease progression. Patients were centrally randomized, using an interactive voice response system, to either immediate ZOL, which was initiated along with adjuvant letrozole, or to delayed ZOL, to be initiated only after 1 of the following events was reported: BMD T-score decreased to < –2.0 at either the LS or TH, any clinical fracture, or an asymptomatic fracture at the 36-month evaluation. Patients who initiated ZOL in both groups received a 6-month dosing schedule of ZOL 4 mg; this schedule was investigational and based on the considerations of tumor burden, accelerated bone loss, and elevated fracture risk in women with EBC receiving adjuvant AIs compared with healthy postmenopausal women. All patients were instructed to take daily oral supplements containing 500 mg calcium and 400-800 IU vitamin D for the study duration. Changes in LS and TH BMD measurements were based on annual DEXA scans analyzed by a central reader.

Patients were stratified according to their established postmenopausal status (postmenopausal vs. recently menopausal), baseline T-score (normal [T-score > –1.0] vs. osteopenic [T-score between ≤ –1.0 and ≥ –2.0]), and previous adjuvant chemotherapy (yes vs. no). The definitions for normal BMD, osteopenia, and osteoporosis were based on definitions provided by the World Health Organization[22] and National Osteoporosis Foundation[23]: normal (T-score ≥ –1), osteopenia (T-score < –1.0 and > –2.5), and osteoporosis (T-score ≤ –2.5).

The institutional review board, independent ethics committee, and research ethics board at each participating center approved this study. Informed consent was obtained from each patient before enrollment, and the study was carried out in compliance with the

Figure 1 CONSORT Diagram



[a]If patients were randomized to the immediate arm but inadvertently did not start ZOL within 4 weeks of randomization, they were considered to be in the delayed ZOL arm for the safety analyses. Conversely, patients in the delayed ZOL group who initiated ZOL within 4 weeks of randomization were considered to be in the immediate ZOL arm for the safety analyses. [b]One patient withdrew consent immediately after being randomized. [c]For 4 patients, documentation showing that they had received study drug was not available. Abbreviations: ITT = intent to treat; ZOL = zoledronic acid.

principles of good clinical practice outlined in the Declaration of Helsinki.

This trial is registered at www.clinicaltrials.gov, No. NCT00171314, and detailed information on study amendments, locations, and dates are available at this web site (http://www.clinicaltrials.gov/ct2/show/NCT00171314).

Study Endpoints and Assessments

The primary endpoint was the percentage change from baseline in the LS (L2-4) BMD between patients in the immediate ZOL group and delayed ZOL group as measured by DEXA scan at 12 months. Secondary endpoints included percentage change from baseline in the LS and TH BMD, clinical fracture incidence, disease recurrence events, and safety. Adverse events (AEs) and disease progression were evaluated every 6 months. DEXA bone scans were performed at baseline; at 6, 12, 24, 36, and 48 months; and at the final visit. AEs were assessed and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.[24] Serum creatinine levels were measured at baseline, before each ZOL infusion, and at the final visit. Renal function deterioration was defined as an increase of at least 0.5 mg/dL in serum creatinine levels for patients with normal baseline serum creatinine levels (< 1.4 mg/dL), an increase of at least 1.0 mg/dL for patients with abnormal baseline serum creatinine levels (≥ 1.4 mg/dL), or a doubling of the baseline serum creatinine value for any patient.

After initiation of the trial, baseline dental health screening for risk assessment of osteonecrosis of the jaw (ONJ) and preventive oral health practices were implemented, as recommended by Weitzman et al.[25] All suspected cases of ONJ were reported as serious AEs and were referred to a dental professional. Diagnoses of ONJ were centrally reviewed by an independent ONJ adjudication committee, consisting of 5 academic experts in the fields of oral and maxillofacial surgery, periodontics, and oral pathology, who were blinded to study treatment assignment for each case adjudicated per established recommendations.[25] ONJ was defined as exposed bone in the maxillofacial area that occurs in association with dental surgery or spontaneously, with no evidence of healing after 6 weeks of appropriate evaluation and dental care and no evidence of metastatic disease in the jaw or osteoradionecrosis.

Statistical Methods and Study Populations

A sample size of 500 was based on practical considerations, and no inferential analyses were planned. Treatment comparisons were 2-sided and made at a significance level of 0.05. The primary analysis included an analysis of covariance (ANCOVA) between the treatment groups. A Student *t* test was used to evaluate treatment differ-

Table 1 Demographic Summary by Treatment Group (Safety Population)

Variable	Immediate ZOL (n = 252)	Delayed ZOL (n = 270)	Total (N = 522)
Age, Median Years (Range)	58 (40-81)	58 (44-78)	58 (40-81)
Race, n (%)			
White	226 (89.7)	242 (89.6)	468 (89.7)
Asian	21 (8.3)	19 (7.0)	40 (7.7)
Other	5 (2.0)	9 (3.3)	14 (2.7)
Baseline T-Score, n (%)			
T-score > –1.0 (normal)	163 (64.7)	180 (66.7)	343 (65.7)
–2.0 ≤ T-score ≤ –1.0 (osteopenic)	89 (35.3)	90 (33.3)	179 (34.3)
Postmenopausal Status, n (%)			
Established Postmenopausal	210 (83.3)	228 (84.4)	438 (83.9)
Recently Postmenopausal	42 (16.7)	42 (15.6)	84 (16.1)
Chemotherapy History, n (%)			
Previous Chemotherapy	131 (52.0)	144 (53.3)	275 (52.7)
No previous Chemotherapy	121 (48.0)	126 (46.7)	247 (47.3)

Abbreviation: ZOL = zoledronic acid.

ence in change from baseline in the LS BMD and for paired data to compare differences within treatment groups in spine and hip BMD. Missing data for BMD at 12 months were imputed using the last observation carried forward method. Shift analysis of BMD T-score categories was conducted using the Pearson χ^2 test. The study was not powered to detect a difference in the incidence of clinical fractures or recurrence of breast disease. The frequency of AEs was reported for both groups. Descriptive statistics were used to report the number of BC relapses, including all deaths.

The intent-to-treat (ITT) population was defined as all patients who underwent randomized treatment assignment and received at least 1 postbaseline efficacy assessment. The safety analysis included all patients who were confirmed to have received at least 1 dose of ZOL or letrozole at the time of analysis; the treatment groups were defined based on the treatment actually received. If patients were randomized to the immediate arm but inadvertently did not start ZOL within 4 weeks of randomization, they were considered to be in the delayed arm for the safety analyses. Conversely, patients randomized to delayed ZOL but who initiated ZOL within 4 weeks of randomization were considered to be in the immediate arm for the safety analyses. All variables analyzed herein were based primarily on the safety population, except for the incidence of disease recurrence events and deaths, which were based on the ITT population.

This study was funded by Novartis Oncology (East Hanover, NJ). The steering committee directed the 12-month data review and analysis; all data analyses were performed by PRA International, Mannheim, Germany. The authors who are Novartis employees attended the steering committee meetings and reviewed the manuscript for scientific and data accuracy.

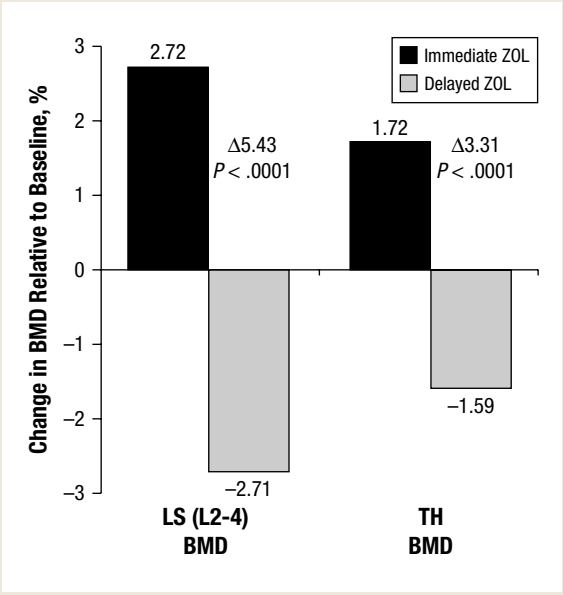
Results

Beginning in March 2004, a total of 527 patients were enrolled and randomized to immediate (263 patients) or delayed ZOL (264 patients) (Figure 1). Patients were enrolled from Europe (n = 464), South America (n = 13), the Middle East (n = 8), Asia-Pacific (n = 32), and South Africa (n = 10). The safety population included 522 patients, of whom 260 were randomized to immediate and 262 to delayed ZOL. In addition, 3 patients randomized to the immediate ZOL group did not receive ZOL within the stipulated 4 weeks after randomization and were, per protocol, assessed as part of the delayed ZOL group. Conversely, 11 patients randomized to the delayed ZOL group received ZOL within 4 weeks after randomization and were assessed as part of the immediate ZOL group. Thus 14 patients did not receive their assigned treatment and therefore 252 and 270 patients were evaluated as having received immediate or delayed ZOL, respectively (Table 1). Treatment arms were well balanced in age, menopausal status, BMD, and previous chemotherapy. The most common reason for patient discontinuation was AEs (22 patients for immediate ZOL [8.7%]; 26 patients for delayed ZOL [9.6%]). Overall, 454 of the 527 total patients (86%) completed the month 12 visit. At month 12, 35 patients (13%) randomized to the delayed ZOL group had initiated ZOL because of a BMD T-score decrease to < –2.0 for either the LS or TH, any clinical fracture, or investigator error; the average time before ZOL initiation in these patients was 8.1 months. The most common reason for ZOL initiation was a spine (L2-4) T-score < –2.0 (n = 25).

BMD Analysis

The mean percentage change from baseline BMD at 12 months (based on treatment received) at the LS was +2.72% for immediate ZOL and −2.71% for delayed ZOL, resulting in a significant absolute difference of 5.43% ($P < .0001$) (Figure 2). Similarly, the mean percentage change from baseline BMD for the TH was +1.72% for immediate ZOL and −1.59% for delayed ZOL, resulting in a significant absolute difference of 3.31% ($P < .0001$). Overall results and statistical significance for differences in BMD change between study arms were consistent when analyzed in the ITT population because more than 97% of patients received their assigned treatment.

Figure 2 Percentage Changes in LS (L2-4) and TH BMD for Patients Receiving Immediate Vs. Delayed ZOL



Abbreviations: BMD = bone mineral density; LS = lumbar spine; TH = total hip; ZOL = zoledronic acid.

Shift in the LS (L2-4) BMD T-score at 12 months was analyzed by baseline BMD status (Figure 3). In patients with normal baseline BMD (n = 294), normal BMD was maintained in 101 patients in the immediate ZOL group (71.1%) and in 87 patients in the delayed ZOL group (57.2%). Additionally, only 3 patients (2.1%) in the immediate ZOL group transitioned to osteopenia, compared with 19 patients (12.5%) in the delayed ZOL group. In patients who were osteopenic at baseline (n = 158), transition to normal BMD status occurred in 13 patients in the immediate ZOL group (18.3%) vs. 7 patients in the delayed ZOL group (8%). No patients with osteopenia at baseline experienced severe osteopenia or osteoporosis with immediate ZOL treatment, compared with 11 patients (12.6%) in the delayed ZOL group who did.

The percentage change from baseline for the primary endpoint (LS BMD)— stratified by postmenopausal status, baseline T-score, and previous chemotherapy status—was also analyzed. In all subgroups, the immediate ZOL group had an increase in BMD (Table 2), and the differences between immediate and delayed ZOL treatment were statistically significant ($P < .0001$ for all). Differences in percentage change from baseline BMD between immediate and delayed ZOL were, however, most profound in recently menopausal patients (6.78%; $P < .0001$) compared with established postmenopausal patients (5.17%; $P < .0001$).

Treatment and Adverse Events

Ten patients required dose modifications of ZOL based on their renal function. Of these, 6 patients had dose reductions after receiving at least one 4-mg dose of ZOL, whereas the other 4 patients initiated ZOL at 3.5 or 3.3 mg, per prescribing information.

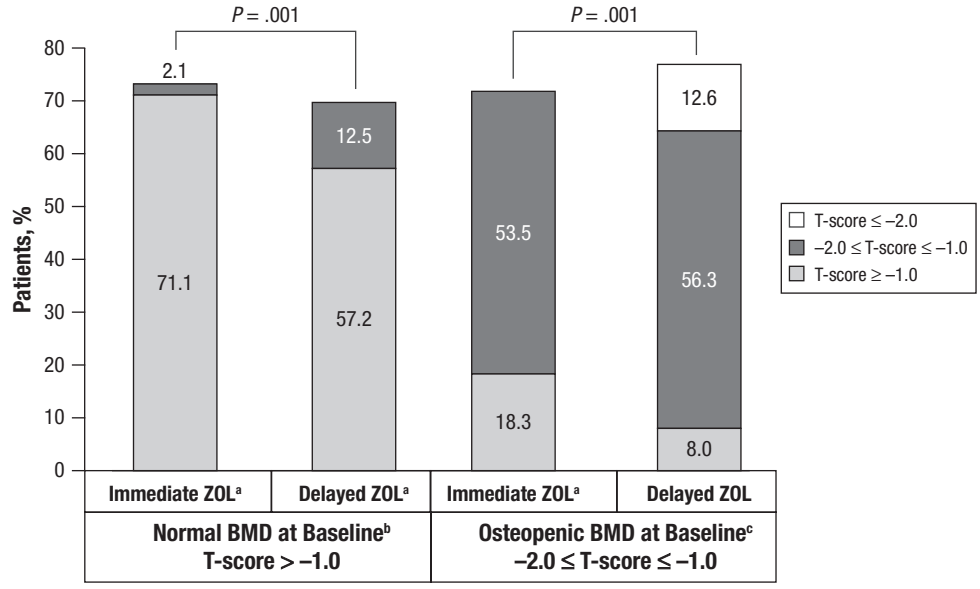
The most common AEs were as expected in this patient population and included arthralgia, hot flushes, fatigue, and myalgias (Table 3). There were no significant imbalances in AEs between the treatment groups, with the exception of bone pain, pain in an extremity, and pyrexia and influenza-like illness that are associated with an acute-phase reaction; these symptoms are most common after the first infusion of nitrogen-containing BPs such as ZOL. All AEs were mild and transient. There was 1 case of renal failure in the immediate ZOL group. This patient had received 3 doses of ZOL 4 mg and withdrew from the study before further follow-up data could be obtained**.** In addition, 3 deaths were reported, all of which occurred in the immediate ZOL group. The cause of death was reported as myocardial infarction (1 patient) and recurrent/progressive breast disease (2 patients). These deaths were not considered by the investigators to be study drug–related. The only case of atrial fibrillation occurred in a patient in the delayed ZOL group who had not received ZOL. Two (0.4%) reported cases of ONJ (both in the immediate ZOL group) were confirmed by the adjudication committee. The patients had received 3 and 6 doses of ZOL, respectively, before the event. In 1 patient, ONJ resolved on discontinuation of ZOL treatment. The second patient with ONJ did not improve despite discontinuation of ZOL treatment.

There were 2 patients (0.8%) with fractures in the immediate ZOL group compared with 5 patients (1.9%) in the delayed ZOL group. Consistent with the short duration of follow-up, the incidence of disease recurrence was low for both groups. At 12 months, 7 patients (2.8%) in the immediate ZOL group and 5 patients (1.9%) in the delayed ZOL group experienced distant recurrent disease. Bone was the predominant site of recurrence, with bone metastases developing in 3 patients in the immediate ZOL group and in 5 patients in the delayed ZOL group. Further follow-up of this patient population is needed for meaningful between-group comparisons of fracture, disease recurrence, and survival rates.

Discussion

This 12-month report from the E-ZO-FAST study confirms, in a more diverse study population, the results reported in the North American Z-FAST[17] and predominantly European ZO-FAST studies[18] on the benefits of immediate ZOL administration in preventing AIBL and maintaining bone health. In Z-FAST and ZO-FAST at 12 months, immediate ZOL treatment significantly increased the LS BMD compared with delayed ZOL treatment ($P < .0001$). Consistent with Z-FAST and ZO-FAST, early intervention with ZOL in patients receiving adjuvant letrozole treatment significantly increased BMD at all sites analyzed in the 12-month assessment of E-ZO-FAST ($P < .0001$). Increases in BMD with immediate ZOL treatment occurred regardless of patients' menopausal status, previous chemotherapy status, or baseline T-score. Moreover more patients with osteopenia receiving immediate ZOL therapy maintained or increased BMD compared with their counterparts who received delayed ZOL treatment. Additionally, no patients in the immediate ZOL group experienced a decline in T-score below –2 by 12 months compared with 11 patients (12.6%) in the delayed ZOL group who did experience that decline. Taken together, the data demonstrate that immediate ZOL treatment with adjuvant letrozole therapy can

Figure 3 Lumbar-Spine BMD Shift From Baseline to Month 12 (Safety Population)



[a]No patients had a T-score < –2.0. [b]Month 12 BMD scores were not available for 38 patients in the immediate ZOL arm and 46 in the delayed ZOL arm in those patients who had a normal baseline T-score. [c]Month 12 BMD scores were not available for 20 patients in the immediate ZOL arm and 20 in the delayed ZOL arm in those patients who were osteopenic at baseline. Abbreviations: BMD = bone mineral density; ZOL = zoledronic acid.

sustain and improve bone health across a broad range of patient demographics.

Immediate and delayed ZOL treatments were generally well tolerated. AEs reported in this study were consistent with those previously reported in the literature. There was no evidence of unexpected combined toxicity between ZOL and letrozole. Importantly this trial is among the first to prospectively evaluate the incidence of ONJ and to institute preventive measures for reducing its occurrence. The incidence of ONJ reported in this study was low (0.4%) and consistent with reported rates in other studies of EBC.[19,20]

Although BMD benefits with immediate vs. delayed ZOL treatment were seen in all patient subsets, recently menopausal women appeared to have larger benefits, perhaps because rates of bone loss are generally increased immediately after menopause. Moreover, chemotherapy-induced menopause, either temporary or permanent, is associated with significant bone loss.[26] Substantial reductions in BMD of the spine and femoral neck have been reported within the first year of adjuvant chemotherapy for BC, which is often ablative to the ovaries.[27,28] Thus it is likely that AI administration may exacerbate the increased bone loss in this patient population, providing a rationale for early initiation of bone-protecting therapy.

The current analysis was based on the 12-month follow-up of BMD data, the primary endpoint of this trial. A consequent limitation of this early data cutoff is that the incidences of fractures and deaths are low at this point in the study. Longer term follow-up of this and the Z-FAST and ZO-FAST studies will provide more definitive insight into the relative efficacy and safety of combining ZOL with letrozole early vs. late in the adjuvant setting in patients with EBC.

Especially rapid bone loss can occur during AI therapy, placing patients at high risk for fractures. Although current guidelines recommend using BP therapy in patients with a T-score ≤ -2.5,[29] more recent guidance considering the latest clinical evidence[7,19,20,30–32] recommended the use of a BP for patients receiving AI therapy if they had any 2 of the following risk factors: T-score < -1.5, age > 65 years, body mass index < 20 kg/m^2, family history of hip fracture, personal history of fragility fracture after age 50 years, corticosteroid use > 6 months, and current or history of smoking, but the relative contributions of these factors and their effects on treatment benefits are unknown.[29] Additional trials of BPs in the AIBL setting, including risedronate (Study of Anastrozole with the Bisphosphonate RisedronatE [SABRE]),[33] and ibandronate (Effect of Oral Ibandronate on Anastrozole-Induced Bone Loss [ARIBON]),[34] are ongoing. Other bone-protecting agents, such as denosumab, are also being investigated in this setting.[35] Longer term follow-up of these trials will provide further guidance for preventing and treating AIBL.

Emerging clinical data suggest that in addition to its bone-protective benefits, ZOL appears to provide anticancer benefit in patients with EBC. Improved cancer outcomes were reported in long-term follow-up (62 months) of the ABCSG-12 trial, wherein patients receiving ZOL experienced a 32% reduced risk of disease-free survival (DFS) events ($P = .009$).[36] These data suggest that the anticancer benefit of ZOL is sustained for at least 2 years after treatment.

Table 2 Changes in BMD at Lumbar Spine and Total Hip by Baseline Stratification Factors (Safety Population)

Variable	Immediate ZOL (n = 252)	Delayed ZOL (n = 270)
Adjusted Percentage Change in Lumbar Spine (L2-4) BMD From Baseline to 12 Months[a]		
Postmenopausal Status		
Established Postmenopausal	+2.78	−2.39
Recently Postmenopausal	+1.72	−5.06
Chemotherapy		
Previous Chemotherapy	+2.33	−3.45
Chemotherapy Naive	+2.90	−2.10
BMD Status		
Normal	+2.42	−3.14
Osteopenic	+3.01	−2.18
Adjusted Percentage Change in Total Hip BMD From Baseline to 12 Months[a]		
Postmenopausal Status		
Established Postmenopausal	+1.77	−1.30
Recently Postmenopausal	+1.25	−3.26
Chemotherapy		
Previous Chemotherapy	+2.18	−1.76
Chemotherapy Naive	+1.23	−1.44
BMD Status		
Normal	+1.58	−1.79
Osteopenic	+1.90	−1.19

Abbreviations: BMD = bone mineral density; ZOL = zoledronic acid.
[a] Difference is model-adjusted estimate assuming a baseline value equal to the overall geometric mean for all patients.

Moreover, data from the extended follow-up of the Z-FAST and ZO-FAST trials support an anticancer benefit associated with early ZOL treatment. In the 36-month follow-up of ZO-FAST, immediate administration of ZOL decreased the risk of disease progression (hazard ratio, 0.588; 95% confidence interval, 0.361-0.959; P = .0314) compared with delayed ZOL administration.[20] A similar, albeit nonsignificant, trend was observed in the 36-month follow-up of the Z-FAST trial, ie, disease recurrence was reported in 16 (5.3%) and 21 (7.0%) patients treated with upfront vs. delayed ZOL, respectively.[37] It should be noted, however, that these similarly designed trials differ in methodologic aspects of evaluating and following disease progression, confounding a pooled analysis of data. In particular, the Z-FAST trial did not systematically follow patients for disease progression or survival status after discontinuation of study medication. Overall these studies support the benefit of ZOL regardless of menopausal status; accordingly, the recent ESMO guidelines recommend ZOL in both pre- and postmenopausal women receiving AIs.[5]

A report from the neoadjuvant substudy (N = 205) of Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE)[38] provides additional evidence of the anticancer benefits of ZOL. In this study, patients receiving ZOL and chemotherapy had a mean 43% reduction in residual tumor volume (P = .006) and an approximate 2-fold improvement in complete pathologic response (6.9% vs. 11.7%; P = .146) compared with patients receiving chemotherapy alone. In a more recent follow-up of the AZURE trial, the observed benefit in tumor response in this neoadjuvant substudy did not translate into DFS benefits for the overall study population (hazard ratio = 0.98; P = .79).[39] However prospective subgroup analyses showed that ZOL significantly improved DFS (hazard ratio = 0.76; $P < .05$) in the subset of women > 5 years past menopause at study entry (n = 1041). In addition, ZOL significantly improved overall survival in women of unknown postmenopausal status but age > 60 years (hazard ratio = 0.71; P = .017; n = 1101). These data suggest that ZOL may augment anticancer benefit in patients with low estrogen levels (relative to premenopausal women) at baseline. Additional data from ongoing trials in the adjuvant BC setting, such as AZURE, Studying the Benefits of Adjuvant Sequential vs Combined Taxane Based Chemotherapy Followed by Different Biological Treatment Strategies in Early, HER2-Positive Breast Cancer (SUCCESS), Postoperative Use of Zoledronic Acid in Breast Cancer Patients After Neoadjuvant Chemotherapy (NATAN), Southwest Oncology Group 0307 (SWOG 0307), A Study to Compare ETC vs EC-TX and Ibandronate vs Observation in Patients With Node-Positive Primary Breast Cancer (GAIN), Study in Elderly Patients With Early Breast Cancer (ICE), Austrian Breast and Colorectal Cancer Study Group trial 18 (ABCSG-18), Study of Denosumab as Adjuvant Treatment for Women With High-Risk Early Breast Cancer Receiving Neoadju-

Table 3 Adverse Events (All Grades) Occurring in > 5% of Patients (Safety Population)

Event	Immediate ZOL	Delayed ZOL	Total
	(n = 252)	(n = 270)	(N = 522)
Any Adverse Event	221 (87.7)	242 (89.6)	463 (88.7)
Arthralgia	90 (35.7)	105 (38.9)	195 (37.4)
Hot Flush	57 (22.6)	85 (31.5)	142 (27.2)
Fatigue	38 (15.1)	50 (18.5)	88 (16.9)
Myalgia	28 (11.1)	28 (10.4)	56 (10.7)
Asthenia	23 (9.1)	21 (7.8)	44 (8.4)
Bone Pain	21 (8.3)	11 (4.1)	32 (6.1)
Pain in Extremity	19 (7.5)	31 (11.5)	50 (9.6)
Nausea	17 (6.7)	14 (5.2)	31 (5.9)
Pyrexia	17 (6.7)	0 (0.0)	17 (3.3)
Influenza-like Illness	15 (6.0)	3 (1.1)	18 (3.4)
Back Pain	13 (5.2)	19 (7.0)	32 (6.1)
Headache	11 (4.4)	19 (7.0)	30 (5.7)
Peripheral Edema	13 (5.2)	16 (5.9)	29 (5.6)
Weight Increase	14 (5.6)	16 (5.9)	30 (5.7)
Shoulder Pain	10 (4.0)	16 (5.9)	26 (5.0)
Lymphedema	14 (5.6)	11 (4.1)	25 (4.8)
Anxiety	9 (3.6)	14 (5.2)	23 (4.4)
Hypertension	13 (5.2)	9 (3.3)	22 (4.2)
Hypercholesterolemia	7 (2.8)	14 (5.2)	21 (4.0)
Depression	5 (2.0)	15 (5.6)	20 (3.8)

Preferred terms are sorted in descending order of frequency.
A patient with multiple occurrences of an adverse event under 1 treatment is counted only once in the adverse event category for that treatment.
Abbreviation: ZOL = zoledronic acid.

vant or Adjuvant Therapy (D-CARE), and others, will provide further insight into the evolving role of antiresorptive therapies in the adjuvant BC setting.

Conclusion

These 12-month E-ZO-FAST results add to the considerable clinical experience of letrozole-ZOL combination therapy in the adjuvant BC setting. Administering ZOL immediately with adjuvant letrozole in postmenopausal women with BC protects and maintains BMD with an acceptable safety profile. Further insight on the role of ZOL in treating AIBL is expected from longer follow-up of patients from this (E-ZO-FAST) and its companion studies (Z-FAST and ZO-FAST).

Clinical Practice Points

- Letrozole is a proven and effective adjuvant therapy in postmenopausal women with hormone receptor–positive (HR^+) early breast cancer.
  - As with other aromatase inhibitors (AIs), long-term letrozole is associated with decreased bone mineral density (BMD) and increased fracture risk.
- Data from companion studies (Z-FAST and ZO-FAST) clearly demonstrated that early initiation of zoledronic acid (ZOL) improves clinical benefit in terms of AI-associated bone loss (AIBL) prevention compared with delayed ZOL in patient populations in North America and Europe, respectively.
  - The current study sought to extend these results to a patient population recruited across a broader geographic region.
- Consistent with Z-FAST and ZO-FAST, early intervention with ZOL in patients receiving adjuvant letrozole treatment significantly increased BMD at all sites analyzed in the 12-month assessment of E-ZO-FAST ($P < .0001$).
  - Increases in BMD with immediate ZOL occurred regardless of patients' menopausal status, prior chemotherapy status, or baseline T-score.
  - Moreover, more patients with osteopenia receiving immediate ZOL maintained or increased BMD compared with their counterparts who received delayed ZOL.
  - Additionally, no patients in the immediate ZOL group experienced severe osteopenia or osteoporosis by 12 months compared with 11 patients (12.6%) in the delayed ZOL group who did.
- Administering ZOL immediately with adjuvant letrozole in postmenopausal women with breast cancer protects and maintains BMD with an acceptable safety profile.
  - These data clearly suggest that ZOL therapy prevents AIBL and that initiation of ZOL therapy should coincide with initiation of AI therapy.

Acknowledgments

The following investigators are acknowledged for their contributions to this study:

E-ZO-FAST investigators—Dr Carlos Silva, Dr Anibal Nunez de Pierro, Dr Francisco Queralt, Dr Jeroen Mebis, Dr Ines Deleu, Dr Lionel Duck, Dr Luc Marcelis, Dr Sabine Marichal, Professor Jan Vermorken, Dr Guy Jerusalem, Dr Luc Verbeke, Dr Frederic Buxant, Professor Luc Baeyens, Dr Frédéric Forget, Professor Patrick Neven, Professor Robert Paridaens, Professor Jacques De Greve, Dr Didier Verhoeven, Dr Wim Wynendaele, Professor Peter van Dam, Dr Outi Paija, Dr Laurence Vanlemmens, Dr Lionel Uwer, Professor Eric Levy, Dr Pierre Kerbrat, Professor Nicole Tubiana-Mathieu, Dr Laurent Cany, Dr Anne-Claire Hardy-Bessard, Dr Laurent Cals, Dr Emmanuelle Bourbouloux, Dr Tamas Pinter, Dr Andras Csejtei, Professor Antonio Contu, Professor Franco Patrone, Dr Gianni Ucci, Dr Laura Merlini, Dr Mario Airoldi, Dr Sergio Bretti, Dr Cesare Gridelli, Dr Claudio Megate, Dr Ugo Folco, Professor Byeong-Woo Park, Professor Soo-Jung Lee, Professor Jung-Han Yoon, Dr Marwan Ghosn, Dr HP Sleeboom, Dr HJT Rutten, Mrs ME Keemers-Gels, Mrs JG Haasjes, Dr Bernado Rapoport, Professor Paul Ruff, Dr J. Raats, Dr Ana Lluch Hernandez, Dr Amparo Ruiz, Dr Montserrat Muñoz, Dr Enrique Aranda, Dr Enrique Ales-Martinez, Dr Dia Trad.

The steering committee members included Dr Carlos Barrios, Dr Adam Brufsky, Professor Nigel Bundred, Dr Ian Campbell, Dr Richard de Boer, Dr Holger Eidtmann, Dr Antonio Frassoldati, Dr Antonio Llombart, Dr Outi Paija, Dr Fatima Cardoso, Dr Robert Coleman, Professor John Forbes, Dr Eun Sook Lee, Dr HP Sleeboom, and Dr Michele Tubiana-Hulin.

Funding for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. We acknowledge Jerome F. Sah, PhD, ProEd Communications, Inc, for his medical editorial assistance with this manuscript.

Disclosure

Antonio Llombart has received honoraria and research grants from Novartis, GlaxoSmithKline, Roche, Sanofi-Aventis, and Genentech, and has received other remuneration from Cephalon.

Outi Paija has received lecture fees and research support from Roche, GlaxoSmithKline, Novartis, and AstraZeneca; is an advisory member for Novartis Nordic group and AstraZeneca Finland; and has given expert testimony for MSD Drugs.

Guy Jerusalem is a consultant for Novartis and receives research funding from Novartis.

Jeroen Mebis has been a consultant for Schering-Plough and GlaxoSmithKline.

Joel Miller was employed by Novartis at the time he worked on this clinical trial, and he owns stock in the company. He is currently employed by ImClone, a wholly owned subsidiary of Eli Lilly.

Nora Schenk is currently employed by Novartis and owns stock in the company.

Antonio Frassoldati, Harm Sleeboom, Ines Deleu, and Patrick Neven have no relevant relationships to disclose.

References

1. Carlson RW, Allred DC, Anderson BO, et al. Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2009; 7:122-92.
2. Thuerlimann B, Koeberle D, Senn HJ. Guidelines for the adjuvant treatment of postmenopausal women with endocrine-responsive breast cancer: past, present and future recommendations. *Eur J Cancer* 2007; 43:46-52.
3. Carlson RW, Hudis CA, Pritchard KI. Adjuvant endocrine therapy in hormone receptor–positive postmenopausal breast cancer: evolution of NCCN, ASCO, and St Gallen recommendations. *J Natl Compr Canc Netw* 2006; 4:971-9.
4. Hadji P. Aromatase inhibitor–associated bone loss in breast cancer patients is distinct from postmenopausal osteoporosis. *Crit Rev Oncol Hematol* 2009; 69:73-82.
5. Aebi S, Davidson T, Gruber G, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21(suppl 5): v9-14.
6. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; 365:60-2.
7. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005; 353:2747-57.
8. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med* 2009; 361: 766-76.
9. Coleman RE, Banks LM, Girgis SI, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; 8:119-27.
10. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. *J Clin Oncol* 2010; 28:3784-96.
11. Bundred NJ. Aromatase inhibitors and bone health. *Curr Opin Obstet Gynecol* 2009; 21:60-7.
12. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, et al. Zoledronic acid prevents cancer treatment–induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2007; 25:820-8.
13. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 2004; 164:1108-12.
14. Siris ES, Brenneman SK, Miller PD, et al. Predictive value of low BMD for 1-year fracture outcomes is similar for postmenopausal women ages 50-64 and 65 and older: results from the National Osteoporosis Risk Assessment (NORA). *J Bone Miner Res* 2004; 19:1215-20.
15. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996; 312: 1254-9.
16. 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* 2008; 9:840-9.
17. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007; 25:829-36.
18. Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor–associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer* 2008; 112:1001-10.
19. Brufsky AM, Bosserman LD, Caradonna RR, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. *Clin Breast Cancer* 2009; 9:77-85.
20. Eidtmann H, de Boer R, Bundred N, et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST study. *Ann Oncol* 2010; 21:2188-94.
21. Zometa® (zoledronic acid) injection [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
22. WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and Management of Osteoporosis: Report of a WHO Scientific Group. WHO Technical Report Series 921. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_921.pdf. Accessed: March 1, 2011.
23. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Available at: http://www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v7.pdf. Accessed: March 1, 2011.
24. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed: March 1, 2011.
25. Weitzman R, Sauter N, Eriksen EF, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients—May 2006. *Crit Rev Oncol Hematol* 2007; 62:148-52.
26. Brufsky AM. Cancer treatment-induced bone loss: pathophysiology and clinical perspectives. *Oncologist* 2008; 13:187-95.
27. 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* 1997; 15:1341-7.
28. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol* 2001; 19:3306-11.
29. Hadji P, Body JJ, Aapro MS, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. *Ann Oncol* 2008; 19:1407-16.
30. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; 369:559-70.
31. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; 360:679-91.
32. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; 97:1262-71.
33. Eastell R, Van Poznak C, Hannon RA, et al. The SABRE (Study of Anastrozole with the Bisphosphonate RisedronatE) study: 12-month analysis. *J Bone Miner Res* 2007; 22(suppl 1):S113: abstract 300.
34. Lester JE, Dodwell D, Purohit OP, et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clin Cancer Res* 2008; 14:6336-42.
35. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008; 26:4875-82.
36. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomized trial. *Lancet Oncol* 2011; 12:631-41.
37. Brufsky A, Harker G, Beck JT, et al. The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: the Z-FAST study 5-year final follow-up. Poster presented at 32nd Annual San Antonio Breast Cancer Symposium. San Antonio, Texas; 2009: abstract 4083.
38. Coleman RE, Winter MC, Cameron D, et al. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer* 2010; 102:1099-105.
39. Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy. *N Engl J Med* 2011. [E-pub ahead of print]. doi: 10.1056/NEJMoa1105195.