European Journal of Cancer 108 (2019) 100–110

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Phase 2 placebo-controlled, single-blind trial to evaluate the impact of oral ibandronate on bone mineral density in osteopenic breast cancer patients receiving adjuvant aromatase inhibitors: 5-year results of the single-centre BONADIUV trial

Lorenzo Livi [a], Vieri Scotti [a], Isacco Desideri [a], Calogero Saieva [b], Sara Cecchini [c], Giulio Francolini [a], Carlotta Becherini [a], Camilla Delli Paoli [a], Luca Visani [a], Viola Salvestrini [a], Maria Laura De Feo [d], Jacopo Nori [e], Marco Bernini [f], Luis Sanchez [f], Lorenzo Orzalesi [f], Simonetta Bianchi [g], Icro Meattini [a,*]

[a] *Radiation Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, Department of Biomedical, Experimental, and Clinical Sciences, University of Florence, Florence, Italy*
[b] *Cancer Risk Factors and Lifestyle Epidemiologyu Unit, Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Florence, Italy*
[c] *Onco-Hematology Unit, Policlinico San Marco-IOB, Zingonia, Bergamo, Italy*
[d] *UOSD Diabetologia Endocrinologia, Ospedale S. Giuseppe, Empoli, Italy*
[e] *Senology Radiology Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy*
[f] *Breast Surgery Unit, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy*
[g] *Pathology Division, Azienda Ospedaliero-Universitaria Careggi, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy*

Received 18 August 2018; received in revised form 6 December 2018; accepted 12 December 2018
Available online 14 January 2019

KEYWORDS
Breast cancer;
Bisphosphonates;
Ibandronate;
Phase 2;

Abstract ***Aim:*** We present the final results of the BONADIUV trial, a single-blind, randomised, placebo-controlled phase 2 study to evaluate the impact of ibandronate treatment on bone mineral density (BMD) in osteopenic women taking aromatase inhibitors (AI).
Patients and methods: Between 2011 and 2014, 171 osteopenic patients were randomised in a 1:1 ratio to receive either placebo or oral monthly ibandronate (150 mg). Treatment duration was 2 years, with 6-month evaluation. Primary end-point was the 2-year lumbar spine (LS)

* *Corresponding author*: Radiation Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Largo G. A., Brambilla 3, 50134 Florence, Italy. Fax: +39 055 4379930.
E-mail address: icro.meattini@unifi.it (I. Meattini).

https://doi.org/10.1016/j.ejca.2018.12.005

Endocrine therapy;
Bone loss;
Survival;
Randomised trial

and total hip (TH) T-score mean differences as measure of BMD variation. Secondary analyses of survival outcomes have been performed at a 5-year median follow-up.
ClinicalTrials.gov identifier: NCT02616744.
Results: Median age of study population was 60.2 years (range 44–75). At the database cut-off time, the median follow-up was 63.3 months (range 2.7–87.3). No difference in terms of T-score was shown at baseline between arms both for TH ($P = 0.61$) and LS ($P = 0.96$). At 2-year follow up, the mean change was statistically significant in favour of ibandronate arm both at TH ($P = 0.0002$) and LS ($P < 0.0001$). No significant difference in terms of adverse events was observed between arms. At a median follow-up of 63.3 months (range 2.7–87.3), the overall survival (OS) rate was 97.5% in the placebo group and 93.0% in the ibandronate arm ($P = 0.19$). The invasive disease-free survival (iDFS) rates did not differ between groups ($P = 0.42$).
Conclusions: Ibandronate compared to placebo improved BMD change in osteopenic women treated with adjuvant AI. Five-year survival analyses showed no difference between arms in terms of OS and iDFS rates.

1. Introduction

Aromatase inhibitors (AI) represent the mainstay of adjuvant treatment for post-menopausal hormone receptor–positive breast cancer (BC) patients. Several randomised trials and meta-analysis demonstrated AI superiority in terms of disease-free survival (DFS) when compared to tamoxifen treatment [1]. However, AI toxicity profile poses a challenge in modern oncology due to oestrogen suppression, especially in patients potentially affected by several comorbidities [2].

AI pivotal trials demonstrated a significant bone mineral density (BMD) loss, with an increased risk of bone fractures after 5 years [3,4], thus impacting on patient's health-related quality of life (HRQoL).

Bisphosphonates represent an effective therapeutic strategy for prevention of skeletal-related events (SRE) in post-menopausal osteoporotic women. In patients affected by advanced BC, bisphosphonates delayed the time of SRE occurrence, reducing bone pain and improving HRQoL [5]. Conversely, it is still debated their use as standard adjuvant treatment for patients with early disease [6,7].

Ibandronate is an active nitrogen-containing bisphosphonate available both in oral and intravenous formulations; it is an active inhibitor of osteoclastic bone resorption and a potential inductor of BC cells apoptosis [8,9]. The monthly oral formulation is an attractive treatment schedule, alternative to intravenous or weekly oral regimen [10].

We present the results of a placebo-controlled, single-blind randomised phase 2 study evaluating the impact of monthly oral ibandronate on BMD loss for osteopenic post-menopausal patients treated with adjuvant AI (BONADIUV trial).

2. Patients and methods

2.1. Study patients

Between January 2011 and May 2014, we screened at the University of Florence (Florence, Italy) 561 patients treated with adjuvant AI for early BC, measuring BMD with basal dual-energy x-ray absorptiometry (DXA) at lumbar spine (LS) and total hip (TH).

Inclusion criteria of the trial were diagnosis of hormone receptor–positive early BC, post-menopausal status, age <75 years and written informed consent. Exclusion criteria were premenopausal status at time of randomization, disorders of bone metabolism, body mass index (BMI) < 18 kg/m^2, chronic use of steroids, use of bisphosphonates at time of randomization, renal disorders, previous bilateral hip fractures or bilateral hip prostheses and psychiatric disorders or any condition preventing from taking oral drugs.

We calculated T-scores with Hologic [11] manufacturer's reference ranges for the LS (L1 to L4) and the National Health and Nutrition Examination Survey III reference range for the femoral neck region [12]. Independent DXA scans review for quality assurance was not performed. The same DXA machine was used over the trial time for all the patients. Screened patients with normal BMD (T score more than −1 at both LS and TH) were excluded from the study, and a follow-up DXA was performed at 2 years. Patients with osteoporosis (T-score less than −2.5 at either LS or TH) were offered bisphosphonate therapy.

2.2. Study design

Patients classified as osteopenic (T-score ≥2.5 and ≤1.0) both at the LS and TH were randomised in a 1:1

ratio to receive either ibandronate 150 mg (oral tablet, every 28 days) or placebo (identical appearance oral tablet, every 28 days) for an overall treatment time of 2 years.

All recruited patients were treated with 5-year AI, vitamin D (4000 IU, weekly) and calcium (500 mg, daily) supplements. All available AI treatments (exemestane, letrozole and anastrozole) were allowed. The CONSORT diagram is shown in Fig. 1.

Ibandronate/placebo capsules were taken in an upright position, first thing in the morning, on an empty stomach and washed down with 100 mL water to minimise the risk of oesophageal irritation; no food or drink (other than water) was consumed for at least 1 h after taking the study medication.

Upon randomization, patients were stratified by number of years since post-menopausal state ($\leq$5 versus $>$5 years) and BMI ($<$25 versus $\geq$25 kg/m^2). Allocation of the patients in the trial arms was conducted by a stratified randomization, using computer-generated randomised permuted blocks within defined post-menopausal and BMI strata.

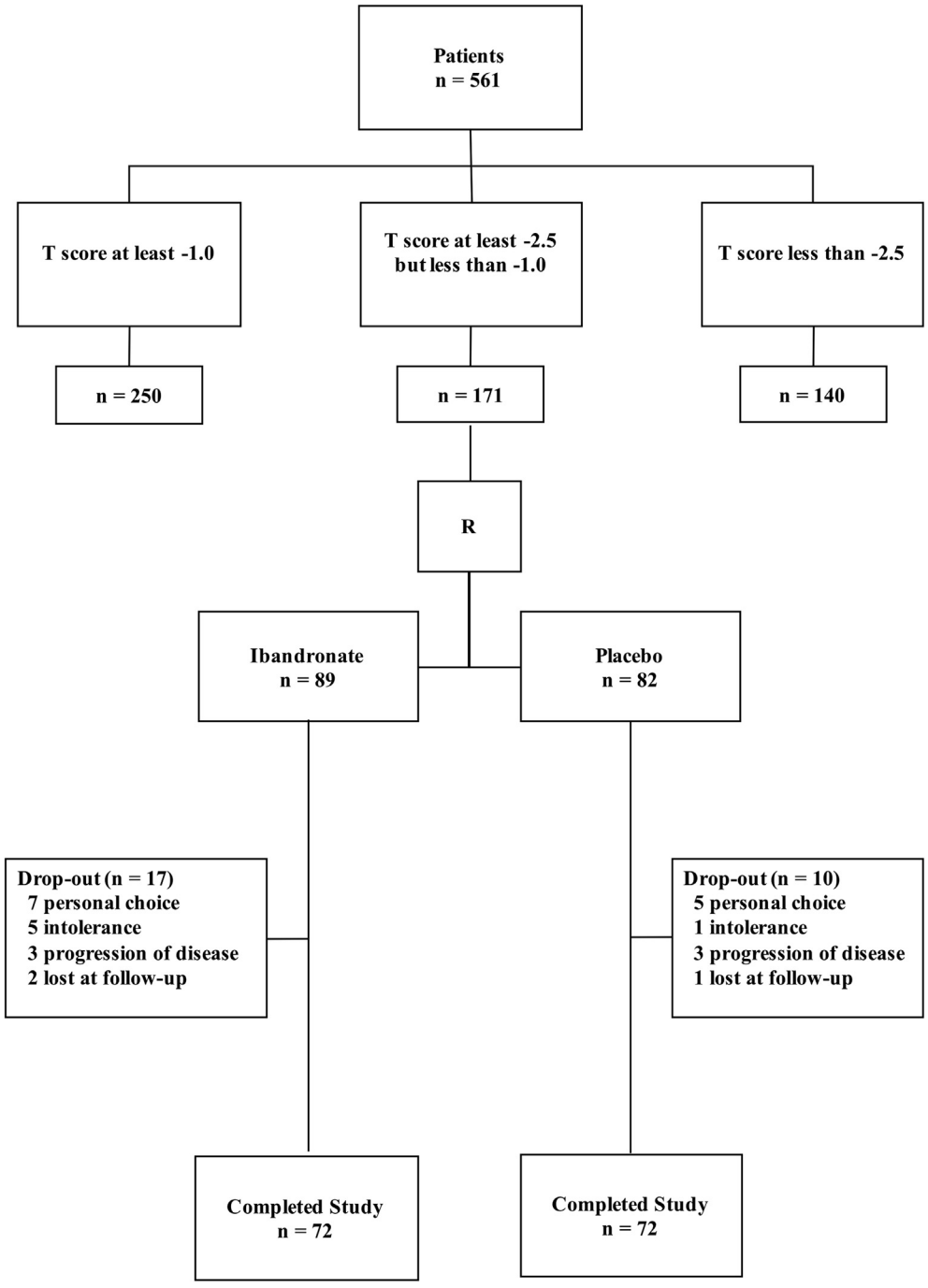

Fig. 1. BONADIUV trial profile (CONSORT diagram).

Primary end-point was the 2-year LS and TH T-score mean differences as measure of BMD variation.

Secondary outcomes were adverse events as a measure of safety and tolerability of treatments, invasive DFS (iDFS; defined as any recurrence of contralateral invasive BC [CBC], locoregional recurrence [LRR], distant metastases [DM]) and overall survival (OS).

We also assessed hematic and urinary calcaemic, phosphoremia, parathormone, magnesemia, vitamin D, urinary pyridinoline, and telopeptide-C at basal, 1 year, and 2 year from randomization (bone turnover biomarkers were not mandatory due to lack in reimbursement from the Italian National Health System; data not reported in the present study). Study duration was 2 years, with 6-month planned evaluations. Patients were followed up every 6 months (years 1–5), then yearly (years 5–10). The NCI Common Terminology Criteria for adverse events, version 4.0 (NCI-CTC v 4.0) was used.

A secondary analysis on survival outcomes has been performed at a median follow-up time of 5.3 years (database cut-off on 4 May 2018). Intention-to-treat (ITT) and per-protocol (PP) analyses of survival outcomes were performed. The study was conducted following the Declaration of Helsinki principles and reviewed by the institutional review board/independent ethics committee. Please refer to this study by its ClinicalTrials.gov identifier: NCT02616744.

2.3. Statistical analysis

A total of 72 patients per arm of treatment were needed to obtain an 85% statistical power to detect a 2% BMD mean difference between the two arms (standard deviation [SD] 4). Considering a 10% dropout rate, at least 158 patients were required. Primary end-point analysis is based on 144 patients (72 per arm) who concluded treatment both at 1 year (T1) and 2 years (T2), excluding drop-out subjects with missing treatment data at follow-up (PP analysis). LS and TH BMD were considered separately. T-scores were described by means and SD at baseline and after 1 and 2 years of treatment. We also reported the mean change from baseline at T1 and T2 time points.

The paired samples t-test was used to compare the means of each score in each group at different time points (T1 and T2) from baseline. The Wilcoxon test was used to compare the means of scores between treatment groups at the beginning of the study (T0). Analysis of covariance (ANCOVA) was used to estimate the mean response as a function of treatment and baseline score measurement to examine the change in T-scores due to treatment from baseline at different time points (T1 and T2) by adjusting for baseline score value. Further analysis adjusted for BMI and years from postmenopausal status were performed. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) with $P < 0.05$ considered statistically significant.

3. Results

3.1. Study population

Eighty-two patients were randomly assigned to the placebo arm and 89 to the ibandronate group (n = 171). Ten patients in the placebo group and 17 patients in the ibandronate group withdrew the allocated arm before any follow-up data collection and so were excluded from the primary end-point analysis (Fig. 1). The final analysis of primary end-point was performed on 144 patients (72 patients per arm).

Median age of study population was 60.2 years (range 44–75). Main series characteristics were well balanced; most of cases were small tumours (<2 cm) with negative nodal status. Concerning tumour biology, 65.5% were grade 1–2 tumours, 82.5% were HER2-negative patients, and the Ki67 proliferative index was below the 20% threshold in the 38% of cases. No patients received adjuvant chemotherapy. Concerning adjuvant endocrine therapy, 121 patients (70.8%) received letrozole (63 ibandronate versus 58 placebo arm), 35 (20.5%) received anastrozole (20 ibandronate versus 15 placebo arm), and 15 (8.7%) received exemestane (six ibandronate versus nine placebo arm). Series features at randomization are reported in Table 1 (ITT analysis) and in Appendix Tables (PP analysis).

At the database cut-off time for the present analysis (4 May 2018), median follow-up was 63.3 months for whole series (mean 61.2; range 2.7–87.3), 64.9 months for the placebo arm (range 33.8–84.0), and 62.2 months for the ibandronate arm (range 24.2–87.3).

Table 1
Main baseline individual characteristics (ITT analysis).

Characteristics	Placebo, N = 82	Ibandronate, N = 89
Median age, years (IQR)	59.6 (53.9; 68.0)	60.5 (54.3; 67.0)
T-score		
Total hip	−1.8 (−3.5, −0.2)	−1.7 (−2.5, 0.5)
Lumbar spine	−1.5 (−4.6, 2.8)	−1.4 (−2.5, 6.2)
BMI groups, n (%)		
<25 kg/m^2	47 (57.3)	54 (60.7)
≥25 kg/m^2	35 (42.7)	35 (39.3)
Years from menopause, n (%)		
≤5	28 (34.1)	30 (33.7)
>5	54 (65.9)	59 (66.3)
Mastectomy	26 (31.7)	21 (31.7)
pT1 tumour size	62 (75.6)	68 (76.4)
Negative nodal status	53 (64.6)	52 (58.4)
Tumor grade 1–2	57 (69.5)	55 (61.8)
Ki67 proliferative index ≥20%	52 (63.4)	54 (60.7)
HER2 positive status	12 (14.6)	18 (20.2)

Abbreviations: BMI, body mass index; HER2, human epidermal growth receptor factor 2; IQR, interquartile range.

3.2. Bone mineral density

No difference in terms of T-score was shown at baseline between arms both for TH ($P = 0.61$) and LS ($P = 0.96$).

At 1-year follow-up, placebo group showed a T-score worsening both at TH (mean change: −0.19) and LS (mean change: −0.13). Conversely, ibandronate group showed a T-score improvement at both sites (+0.09 and +0.17 at TH and LS, respectively). The mean change was statistically significant both at TH ($P = 0.0006$) and LS ($P = 0.0001$).

At 2-year follow-up, placebo group showed a T-score decrease at TH (mean change: −0.09), and LS (mean change: −0.24). Ibandronate group showed a T-score increase (+0.28 at TH and +0.35 at LS). The mean change was statistically significant both at TH ($P = 0.0002$) and LS ($P < 0.0001$).

Relative and absolute change of patients' T-scores at TH and LS over time (at T1 and T2) compared with baseline are reported in Table 2 and Table 3, respectively. Percentage changes in TH and LS BMD are shown in Fig. 2 and Fig. 3, respectively. ANCOVA adjusted for BMI and years from post-menopausal status confirmed the results at T1 ($P = 0.021$) and T2 ($P < 0.0001$) for LS, and at T1 ($P = 0.012$) and T2 ($P = 0.09$) for TH.

3.3. Safety

The most represented adverse events recorded during the allocated treatment time were arthralgia/myalgia (43.7%), dyspepsia (18.7%), flu-like symptoms (7.6%) and hot flashes (5.5%). No significant difference was observed between arms (PP analysis). Any grade and severity of main adverse events stratified by arms were summarised in Table 4.

At the time of the present analysis, we recorded two SREs (1.4% in the overall series; one case in the ibandronate arm, and one case in the placebo arm) and five cardiac events (3.5% in the overall series; four in the ibandronate arm [5.6%] and one in the placebo arm [1.4%]; Fisher's exact test 0.37). No osteonecrosis of the jaw occurrence was reported.

3.4. Survival outcome

At the database cut-off time, the OS rate was 97.5% in the placebo group and 93.0% in the ibandronate arm (ITT analysis). We observed six LRR (four in the placebo arm, two in the ibandronate arm; $P = 0.37$), seven DM (one in the placebo arm, six in the ibandronate arm; $P = 0.067$), and three CBC (one in the placebo arm, two in the ibandronate arm; $P = 0.71$). The iDFS events rate did not differ between groups: six in the placebo group and ten in the ibandronate group ($P = 0.42$). Up to data cut-off, eight deaths have occurred: two in the placebo

Table 2
Mean (and SD) T-score at total hip at different time points (baseline, T1 and T2), and change (mean and 95% CI; percentage) at T1 and T2 compared to baseline (per protocol analysis; data available for 144 patients at each assessment time).

Total hip	Baseline	T1				T2			
	Mean (SD)	Mean (SD)	Mean change (95% CI)	Change (%)	*P* value[a]	Mean (SD)	Mean change (95% CI)	Change (%)	*P* value[a]
Placebo arm	−1.76 (0.58)	−1.95 (0.70)	−0.19 (−0.05/−0.33)	−10.8	0.007	−1.85 (0.77)	−0.09 (−0.24/+0.08)	−5.1	0.30
Ibandronate arm	−1.69 (0.58)	−1.60 (0.56)	+0.09 (−0.04/+0.21)	+5.3	0.16	−1.41 (0.68)	+0.28 (0.15/0.40)	+16.6	<0.0001
P value	0.61[b]	0.0006[c]				0.0002[c]			

Abbreviations: CI, confidence interval; SD, standard deviation.
[a] *P*-value from paired samples *t*-test (comparison of repeated measures from baseline at T1 and T2) for each arm.
[b] *P* value from Wilcoxon test (comparison between arms at baseline).
[c] *P* value from covariance analysis (comparison between arms at T1 and T2).

Table 3
Mean (and SD) T-score at lumbar spine at different time points (baseline, T1 and T2), and change (mean and 95% CI; percentage) at T1 and T2 compared to baseline (per protocol analysis; data available for 144 patients at each assessment time).

Lumbar spine	Baseline	T1				T2			
	Mean (SD)	Mean (SD)	Mean change (95% CI)	Change (%)	*P* value[a]	Mean (SD)	Mean change (95% CI)	Change (%)	*P* value[a]
Placebo arm	−1.48 (0.97)	−1.61 (1.06)	−0.13 (−0.05/0.22)	−8.8	0.003	−1.72 (1.07)	−0.24 (−0.14/−0.36)	−16.2	<0.0001
Ibandronate arm	−1.50 (0.77)	−1.33 (0.83)	+0.17 (0.04/0.31)	+11.3	0.01	−1.15 (0.87)	+0.35 (−0.21/0.51)	+23.3	<0.0001
P value	0.96[b]	0.0001[c]				<0.0001[c]			

[a] *P* value from paired Sample *t*-test (comparison of repeated measures from baseline at T1 and T2) for each arm.
[b] *P* value from Wilcoxon test (comparison between arms at baseline).
[c] *P* value from covariance analysis (comparison between arms at T1 and T2).

arm and six in the ibandronate arm. The OS rate did not differ between arms ($P = 0.19$).

The 5-year OS rates were 93.0% (ibandronate arm) versus 97.5% (placebo arm), the 5-year iDFS rates were 89.4% (ibandronate arm) versus 92.4% (placebo arm). Kaplan–Meier OS and iDFS curves are shown in Fig. 4 and Fig. 5, respectively (ITT analysis). PP analyses are reported in Appendix Tables.

4. Discussion

4.1. BMD and safety

The AI impact on patients' HRQoL represents one of the most important challenges in BC adjuvant treatment management due to several potential adverse events, such as sexual dysfunction, cognitive impairment, cardiovascular toxicity, and osteoporosis [13]. Progressive bone loss and potential subsequent SREs related to AI therapy can develop within the first year and continue throughout the duration of endocrine treatment [4,14,15]. Therefore, a bone loss prevention strategy, with the consequent impact on the socio-economical aspects, represents a big concern during this global economic world crisis era. The available evidence suggest that pre- and post-menopausal patients may receive clinical benefit including bisphosphonates as part of their adjuvant treatment regimen for hormone receptors–positive early BC [16,17].

An important debated issue was to clarify the real impact of AI in the BMD decrease, studying the trend of bone loss over time. Indeed, it is well known that post-menopausal patients had several factors (i.e. age, BMI, habits, drugs assumption) that may negatively influence the BMD during endocrine treatment.

Our phase 2 placebo-controlled study showed no difference in TH and LS T-scores at baseline in both arms. At 1-year follow-up, in the placebo arm, we noted a significant T-score worsening at both anatomical sites, in contrast with patients treated with monthly ibandronate. At 2-year control, we reinforced the results: the placebo arm showed a progressive decrease, unlike ibandronate group that continuously increase BMD value. This significant effect was maintained irrespectively of potential confounding factors, such as post-menopausal state and BMI.

Similarly, Lester and colleagues [18] evaluated BMD in 131 post-menopausal, surgically treated early BC (including 50 osteopenic patients) treated with anastrozole and calcium plus vitamin D supplementation. Patients were randomised to receive either treatment with ibandronate 150 mg orally every month or placebo. After 2 years, osteopenic patients treated with ibandronate gained +2.98% and +0.60% at the LS and TH, respectively. Conversely, patients treated with placebo

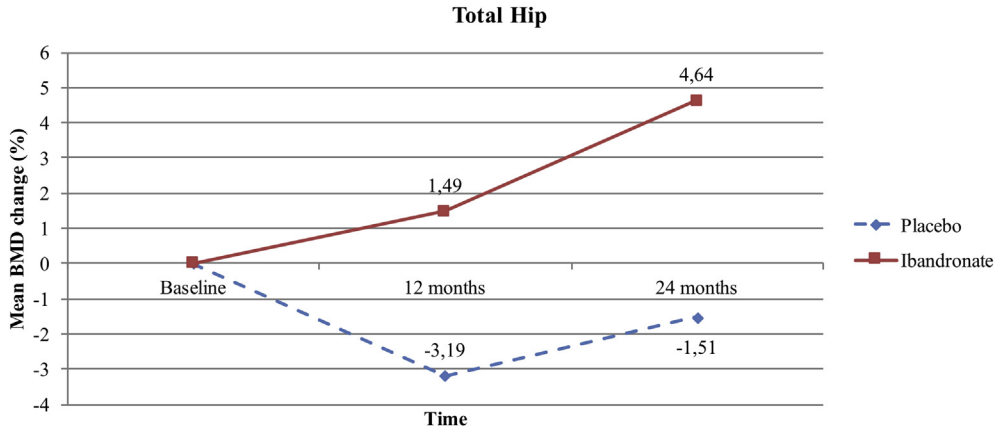

Fig. 2. Bone mineral density (BMD) changes at total hip (144 patients at each time).

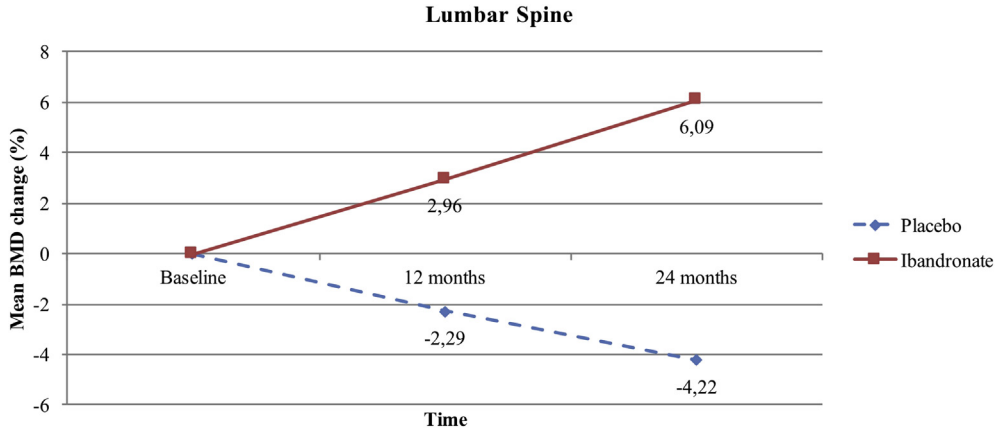

Fig. 3. Bone mineral density (BMD) changes at lumbar spine (144 patients at each time).

Table 4
Main adverse events per arm (per protocol analysis).

Symptom	Ibandronate (n = 72)		Placebo (n = 72)	
	All grades n (%)	Grade ≥2 n (%)	All grades n (%)	Grade ≥2 n (%)
Arthralgia/bone pain/myalgia	31 (43.1)	3 (4.2)	32 (44.4)	2 (2.8)
Dyspepsia	13 (18.1)	1 (1.4)	14 (19.4)	2 (2.8)
Flu-like symptoms	8 (11.1)	0	3 (4.2)	0
Hot flashes	5 (6.9)	0	3 (4.2)	0
Vaginal dryness	4 (5.6)	0	0	0
Mood disorders	4 (5.6)	1 (1.4)	3 (4.2)	1 (1.4)
Dizziness	3 (4.2)	2 (2.8)	1 (1.4)	0
Insomnia	3 (4.2)	0	2 (2.8)	0
Diarrhea	2 (2.8)	0	2 (2.8)	0
Weight gain	2 (2.8)	1 (1.4)	1 (1.4)	0
Breast pain	2 (2.8)	0	3 (4.2)	1 (1.4)
Headache	2 (2.8)	0	3 (4.2)	1 (1.4)
Thromboembolic event	1 (1.4)	0	1 (1.4)	0
Anemia	1 (1.4)	0	1 (1.4)	0
Uterine polyps	1 (1.4)	0	1 (1.4)	0
Overall	**Ibandronate, n (%)**		**Placebo, n (%)**	***P* value**[a]
Any toxicity, any grade	36 (50)		39 (54.2)	0.74
Any toxicity, grade ≥2	7 (9.7)		7 (9.7)	1.0

[a] *P* value from chi-square test.

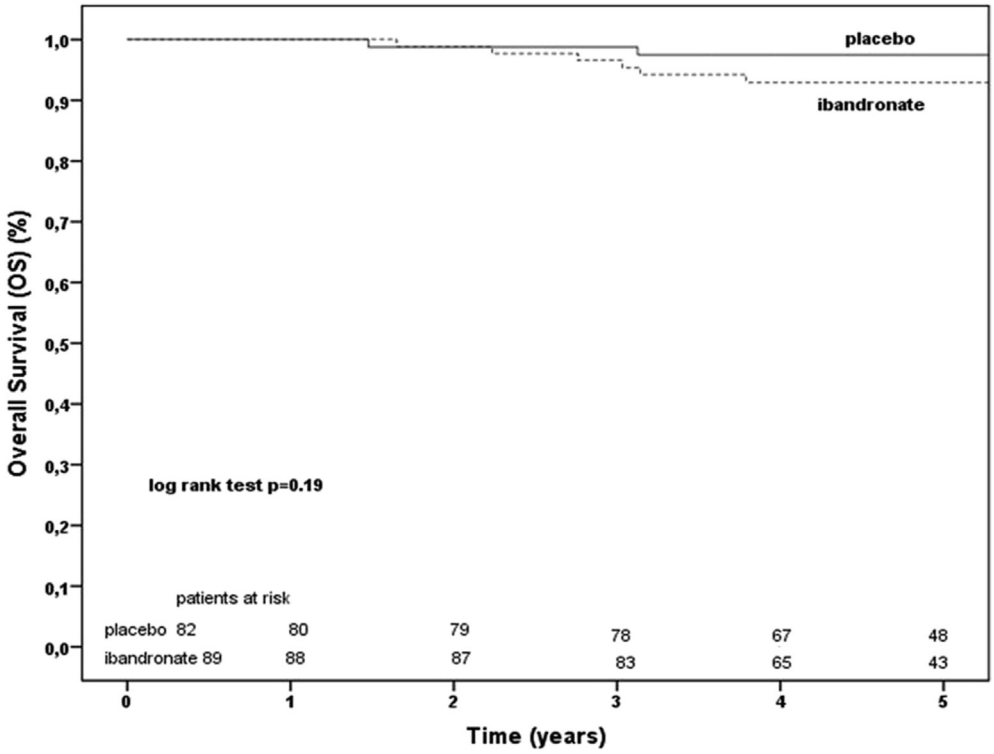

Fig. 4. Kaplan–Meier overall survival (OS) curves by allocated treatment arm (ITT analysis).

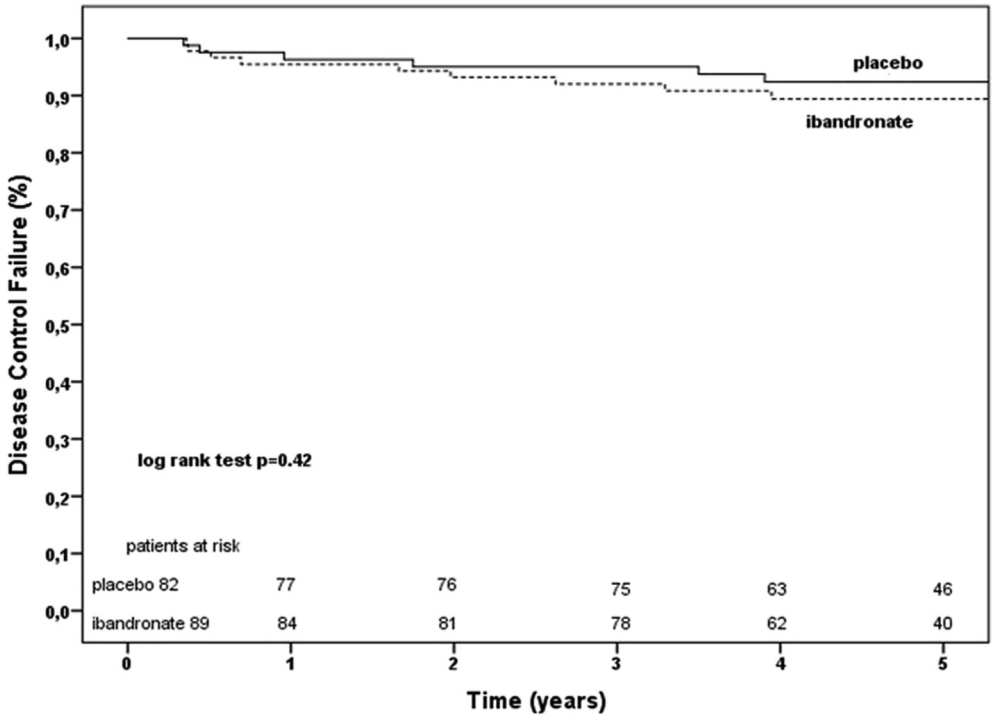

Fig. 5. Kaplan–Meier invasive disease-free survival (iDFS) curves by allocated treatment arm (ITT analysis).

lost −3.22% at the LS and −3.90% at the TH. The differences between the two treatment arms were statistically significant at both sites ($P < 0.01$). At a study update [19], among the 16 patients randomised to placebo, 8 of 16 with high rates of bone loss during years 0–2 received ibandronate over the next 3 years with improvements in BMD of +5.01 and +1.19 at the LS and TH, respectively.

In our experience, bisphosphonates patients compared to baseline showed a 2-year BMD improvement of 4–6% both at TH and LS, with a mean difference between arms much greater than the 2% threshold used for primary end-point statistical assumption. To note, the increase of BMD was almost doubled between 1-year and 2-year follow-up controls.

Ibandronate was not the only bisphosphonate that demonstrated a significant impact on BMD loss prevention strategy. Trials evaluating early assumption of adjuvant zoledronic acid [20–24] and risedronate [25–27] showed a statistically significant improvement of BMD and a bone loss prevention over time.

In our study, patients' treatment tolerance was in line with previously published experiences [28,29], with an expected dropout rate of 19.1% mainly due to patient's personal choice (41.2%) more than tolerance (29.4%) in the treatment arm (Fig. 1). No major adverse events were recorded during study's conduction, the main reported toxicities were arthralgia/myalgia and dyspepsia, with no significant differences between arms observed.

Although the use of the same manufacturer for BMD evaluation and a local reassessment of BMD data performed after database lock, an independent external review for quality assurance purpose was not performed, and this may represent a study limitation.

4.2. Survival outcomes

In our study, at a median follow-up time of 5.3 years, the number of iDFS events and deaths did not differ between arms. However, we are aware of the paucity of events and the short observation time.

Several prospective studies postulated the efficacy of bisphosphonate on BC relapse [30–40]. Powles and colleagues randomised 1069 patients to receive 2 years of oral clodronate or placebo, concomitantly with standard treatment. Results showed that risk of bone metastases was significantly reduced in the experimental arm over the 2- and 5-year medication period (hazard ratio [HR] 0.546, $P = 0.031$ and HR 0.692, $P = 0.043$, respectively), and survival was improved in patients undergoing clodronate treatment (HR 0.768, $P = 0.048$) [30]. Also, findings from the NSABP B-34 trial suggested that bisphosphonates might have anticancer benefits for older post-menopausal women [31]. In the Austrian Breast and Colorectal Cancer Study Group-12 study, a 36% reduction in risk of disease recurrence in premenopausal patients receiving zoledronic acid plus endocrine therapy compared with endocrine therapy alone was observed [32].

Conversely, the results from the 5-year AZURE study [33], which evaluated 3360 patients receiving neoadjuvant chemotherapy and/or endocrine therapy randomised to receive or not receive zoledronic acid indicate that no overall benefit in terms of iDFS from the addition of zoledronic acid to standard adjuvant treatments for early BC. However, it reduced the development of bone metastases and, for post-menopausal women, improved disease outcomes (development of bone metastases, both as a first event and at any time during follow-up), independently of oestrogen-receptor status. Other studies failed to show clinical benefit from bisphosphonates treatment both in the adjuvant (in terms of iDFS or OS) [34–36] and neoadjuvant settings (in terms of DFS and pathological complete response) [37–40].

Even though the results from main published trials evaluating bisphosphonates effects on disease recurrence and survival in BC are conflicting, several countries recommend the use of bisphosphonates as bone metastases prevention strategy for high-risk adjuvant BC.

Reliable evidence is needed about the effects of bisphosphonates on BC outcomes. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2015 meta-analyses showed that adjuvant bisphosphonate treatment in early BC can reduce the rate of disease recurrence in the bone and improve the disease-specific survival in the women who were post-menopausal when treatment began [41]. The EBCTCG meta-analyses update is pending and may confirm these encouraging findings.

5. Conclusions

Two-year adjuvant ibandronate compared to placebo improved BMD change in osteopenic women treated with adjuvant AI. Our results strengthen the overall usefulness of a bone loss prevention strategy for BC patients receiving adjuvant AI, also for the specific group of osteopenic women at baseline. Longer follow-up and further investigations are warranted to monitoring the risk of SRE and survival outcomes in healthy patients treated with AI.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

Acknowledgments

Partial data of the trial were presented at 2013 ESMO Congress cited as Ann Oncol (2013) 24 (suppl 3):iii16 https://doi.org/10.1093/annonc/mdt079.1, at 2014 ASCO Annual Meeting cited as 2014 (suppl; abstr TPS658), and at 2016 San Antonio Breast Cancer Symposium (P2-09-12: A single-blind, randomized, placebo-

controlled phase II study to evaluate the impact of oral ibandronate on bone mineral density in osteopenic breast cancer patients receiving adjuvant aromatase inhibitors: Final results of the single-center BONADIUV trial. Livi L, Saieva C, Desideri I, Scotti V, De Luca Cardillo C, Carta G, Cecchini S, Orzalesi L, Sanchez LJ, Casella D, Bernini M, Nori J, Bianchi S, De Feo ML, Meattini I).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.005.

References

[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomized trials. Lancet 2015;386(10001):1341–52. https://doi.org/10.1016/S0140-6736(15)61074-1.

[2] Kemp A, Preen DB, Saunders C, Boyle F, Bulsara M, Holman CD, et al. Women commencing anastrozole, letrozole or tamoxifen for early breast cancer: the impact of comorbidity and demographics on initial choice. PLoS One 2014;9(1):e84835. https://doi.org/10.1371/journal.pone.0084835.

[3] Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 2010;11(12):1135–41. https://doi.org/10.1016/S1470-2045(10)70257-6.

[4] Thurlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, Forbes JF. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353(26):2747–57. https://doi.org/10.1056/NEJMoa052258.

[5] Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2012;(2):CD003474. https://doi.org/10.1002/14651858.CD003474.pub3.

[6] Hadji P, Aapro MS, Body JJ, Bundred NJ, Brufsky A, Coleman RE, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol 2011;22(12):2546–55. https://doi.org/10.1093/annonc/mdr017.

[7] Jacobs C, Amir E, Paterson A, Zhu X, Clemons M. Are adjuvant bisphosphonates now standard of care of women with early stage breast cancer? A debate from the Canadian Bone and the Oncologist New Updates meeting. J Bone Oncol 2015;4(2):54–8. https://doi.org/10.1016/j.jbo.2015.06.001.

[8] Devitt B, McLachlan SA. Use of ibandronate in the prevention of skeletal events in metastatic breast cancer. Ther Clin Risk Manag 2008;4(2):453–8.

[9] Journé F, Kheddoumi N, Chaboteaux C, Duvillier H, Laurent G, Body JJ. Extracellular calcium increases bisphosphonate-induced growth inhibition of breast cancer cells. Breast Cancer Res 2008;10(1):R4. https://doi.org/10.1186/bcr1845.

[10] Clemons M, Verma S. Should oral bisphosphonates be standard of care in women with early breast cancer? Breast Cancer Res Treat 2005;90(3):315–8. https://doi.org/10.1007/s10549-004-4259-3.

[11] Kelly TL. Bone mineral density reference databases for American men and women. J Bone Miner Res 1990;5(suppl 1):S249.

[12] Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8(5):468–89.

[13] Lintermans A, Neven P. Safety of aromatase inhibitor therapy in breast cancer. Expert Opin Drug Saf 2015;14(8):1201–11. https://doi.org/10.1517/14740338.2015.1053458. Epub 2015 Jun 9.

[14] Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, 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(9453):60–2. https://doi.org/10.1016/S0140-6736(04)17666-6.

[15] Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, 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(9561):559–70. https://doi.org/10.1016/S0140-6736(07)60200-1.

[16] Gnant M, Blaha P, Dubsky P, Exner R, Fitzal F, Sporn E, et al. Adjuvant bisphosphonates in endocrine-responsive breast cancer: what is their place in therapy? Ther Adv Med Oncol 2009;1(3):123–36. https://doi.org/10.1177/1758834009344594.

[17] Gnant M, Clezardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. Cancer Treat Rev 2012;38(5):407–15. https://doi.org/10.1016/j.ctrv.2011.09.003.

[18] Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R, 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(19):6336–42. https://doi.org/10.1158/1078-0432.CCR-07-5101.

[19] Lester JE, Dodwell D, Brown JE, Purohit OP, Gutcher SA, Ellis SP, et al. Prevention of anastrozole induced bone loss with monthly oral ibandronate: final 5 year results from the ARIBON trial. J Bone Oncol 2012;1(2):57–62. https://doi.org/10.1016/j.jbo.2012.06.002.

[20] Nuzzo F, Gallo C, Lastoria S, Di Maio M, Piccirillo MC, Gravina A, et al. Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBOE study. Ann Oncol 2012;23(8):2027–33. https://doi.org/10.1093/annonc/mdr600.

[21] Hines SL, Mincey B, Dentchev T, Sloan JA, Perez EA, Johnson DB, et al. Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. Breast Cancer Res Treat 2009;117(3):603–9. https://doi.org/10.1007/s10549-009-0332-2.

[22] Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Kainberger F, Kässmann H, Piswanger-Sölkner JC, 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(9):840–9. https://doi.org/10.1016/S1470-2045(08)70204-3.

[23] Wagner-Johnston ND, Sloan JA, Liu H, Kearns AE, Hines SL, Puttabasavaiah S, et al. 5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (alliance) trial. Cancer 2015;121(15):2537–43. https://doi.org/10.1002/cncr.29327.

[24] Takahashi S, Iwase T, Kohno N, Ishikawa T, Taguchi T, Takahashi M, et al. Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 12-month. Breast Cancer Res Treat 2012;133(2):685–93. https://doi.org/10.1007/s10549-012-1973-0.

[25] Greenspan SL, Bhattacharya RK, Sereika SM, Brufsky A, Vogel VG. Prevention of bone loss in survivors of breast cancer: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab 2007;92(1):131–6. https://doi.org/10.1210/jc.2006-1272.

[26] Greenspan SL, Vujevich KT, Brufsky A, Lembersky BC, van Londen GJ, Jankowitz RC, et al. Prevention of bone loss with risedronate in breast cancer survivors: a randomized, controlled clinical trial. Osteoporos Int 2015;26(6):1857–64. https://doi.org/10.1007/s00198-015-3100-7.

[27] Sestak I, Singh S, Cuzick J, Blake GM, Patel R, Gossiel F, et al. Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial. Lancet Oncol 2014;15(13):1460–8. https://doi.org/10.1016/S1470-2045(14)71035-6.

[28] Pyon EY. Once-monthly ibandronate for postmenopausal osteoporosis: review of a new dosing regimen. Clin Ther 2006;28(4):475–90. https://doi.org/10.1016/j.clinthera.2006.04.006.

[29] Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005;20(8):1315–22. https://doi.org/10.1359/JBMR.050313.

[30] Powles T, Paterson A, McCloskey E, Schein P, Scheffler B, Tidy A, et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. Breast Cancer Res 2006;8(2):R13. https://doi.org/10.1186/bcr1384.

[31] Paterson AH, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. Lancet Oncol 2012;13(7):734–42. https://doi.org/10.1016/S1470-2045(12)70226-7.

[32] Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360(7):679–91. https://doi.org/10.1056/NEJMoa0806285.

[33] Coleman R, Cameron D, Dodwell D, Bell R, Wilson C, Rathbone E, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. Lancet Oncol 2014;15(9):997–1006. https://doi.org/10.1016/S1470-2045(14)70302-X.

[34] Mardiak J, Bohunický L, Chovanec J, Sálek T, Koza I. Adjuvant clodronate therapy in patients with locally advanced breast cancer–long term results of a double blind randomized trial. Slovak Clodronate Collaborative Group. Neoplasma 2000;47(3):177–80.

[35] von Minckwitz G, Möbus V, Schneeweiss A, Huober J, Thomssen C, Untch M, et al. German adjuvant intergroup node-positive study: a phase III trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer. J Clin Oncol 2013;31(28):3531–9. https://doi.org/10.1200/JCO.2012.47.2167.

[36] Vliek SB, Meershoek-Klein Kranenbarg E, van Rossum AGJ, Tanis BC, Putter H, van der Velden AWG, et al. Abstract S6-02: the efficacy and safety of the addition of ibandronate to adjuvant hormonal therapy in postmenopausal women with hormone-receptor positive early breast cancer. First results of the TEAM IIB trial (BOOG 2006-04). Cancer Research 2017;77:S02–6. https://doi.org/10.1158/1538-7445.SABCS16-S6-02.

[37] Fasching PA, Jud SM, Hauschild M, Kümmel S, Schütte M, Warm M, et al. FemZone trial: a randomized phase II trial comparing neoadjuvant letrozole and zoledronic acid with letrozole in primary breast cancer patients. BMC Cancer 2014;14:66. https://doi.org/10.1186/1471-2407-14-66.

[38] Charehbili A, van de Ven S, Smit VT, Meershoek-Klein Kranenbarg E, Hamdy NA, Putter H, et al. Addition of zoledronic acid to neoadjuvant chemotherapy does not enhance tumor response in patients with HER2-negative stage II/III breast cancer: the NEOZOTAC trial (BOOG 2010-01). Ann Oncol 2014;25(5):998–1004. https://doi.org/10.1093/annonc/mdu102.

[39] Hasegawa Y, Tanino H, Horiguchi J, Miura D, Ishikawa T, Hayashi M, et al. Randomized controlled trial of zoledronic acid plus chemotherapy versus chemotherapy alone as neoadjuvant treatment of HER2-negative primary breast cancer (JONIE study). PLoS One 2015;10(12):e0143643. https://doi.org/10.1371/journal.pone.0143643.

[40] von Minckwitz G, Rezai M, Tesch H, Huober J, Gerber B, Zahm DM, et al. Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer - the Phase III NeoAdjuvant Trial Add-oN (NaTaN) study (GBG 36/ABCSG 29). Eur J Cancer 2016;64:12–21. https://doi.org/10.1016/j.ejca.2016.05.015.

[41] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015;386(10001):1353–61. https://doi.org/10.1016/S0140-6736(15)60908-4.