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Platinum Priority – Prostate Cancer

*Editorial by Bertrand Tombal on pp. 492–494 of this issue*

# Prevention of Bone Metastases in Patients with High-risk Nonmetastatic Prostate Cancer Treated with Zoledronic Acid: Efficacy and Safety Results of the Zometa European Study (ZEUS)

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## Abstract

***Background:*** Patients with high-risk localised prostate cancer (PCa) are at risk of developing bone metastases (BMs). Zoledronic acid (ZA) significantly reduces the incidence of skeletal complications in castration-resistant metastatic PCa versus placebo.
***Objective:*** To investigate ZA for the prevention of BMs in high-risk localised PCa.
***Design, setting, and participants:*** Randomised open-label multinational study with patients having at least one of the following: prostate-specific antigen ≥20 ng/ml, node-positive disease, or Gleason score 8–10.
***Intervention:*** Standard PCa therapy alone or combined with 4 mg ZA intravenously every 3 mo for ≤4 yr.
***Outcome measurements and statistical analysis:*** BMs were assessed using locally evaluated bone-imaging procedures (BIPs), with subsequent blinded central review. Patients with BMs, time to BMs, overall survival, and adverse events were compared between treatment groups.
***Results and limitations:*** A total of 1393 of 1433 randomised patients were used for intention-to-treat (ITT) efficacy analyses, with 1040 patients with BIP-BM outcome status at 4 ± 0.5 yr. The local urologist/radiologist diagnosed BIP-BMs in 88 of 515 patients (17.1%) in the ZA group and 89 of 525 patients (17.0%) in the control group (chi-square test: $p = 0.95$), with a difference between proportions of 0.1% (95% confidence interval [CI], −4.4 to 4.7) in favour of the control group. In the ITT population ($n = 1393$), the Kaplan-Meier estimated proportion of BMs after a median follow-up of 4.8 yr was 14.7% in the ZA group versus 13.2% in the control group (log-rank: $p = 0.65$). Low hot spot numbers on bone scans were confirmed as metastases with additional imaging. Central reviews of BIPs were possible only on a subset of patients.
***Conclusions:*** ZA administered every 3 mo was demonstrated to be ineffective for the prevention of BMs in high-risk localised PCa patients at 4 yr.
***Patient summary:*** Zoledronic acid administered every 3 mo was demonstrated to be ineffective for the prevention of bone metastases in high-risk nonmetastatic PCa patients at 4 yr.
***Trial registration:*** The ZEUS trial is registered in the Dutch trial register www.trialregister.nl and the ISRCTN register at http://www.controlled-trials.com/ISRCTN66626762.

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## 1. Introduction

Prostate cancer (PCa) is characterised by its propensity for bone metastases (BMs) that occur in >80% of patients with advanced PCa [1]. BMs result in morbidity and are associated with pain, pathologic fractures, and decreased survival. The standard treatment of patients with metastases is androgen deprivation therapy (ADT) using surgical or medical castration. The 5-yr survival rate of patients with metastatic or locally advanced disease subjected to ADT is 35% [2]. If considerable numbers of PCa patients receive prolonged ADT, decreased bone mineral density, increased risk for osteoporosis, and skeletal fractures can ensue [2,3].

Accumulating clinical evidence has confirmed the value of bisphosphonates (BPs) in BMs, preventing ADT-related bone loss, reducing morbidity and pain, and improving survival in patients with castration-resistant PCa (CRPC) [4–7]. Zoledronic acid (ZA; Zometa, Novartis, Basel, Switzerland), developed as a third-generation nitrogen-containing BP with increased potency relative to other BPs, induces direct inhibition of PCa cells in vitro, activation of cytotoxic T cells toward a range of malignant cell types, and inhibition of tumour-mediated angiogenesis that may render the bone microenvironment less conducive to micrometastatic growth [8–11].

We investigated the efficacy of 3-mo ZA for BM prevention in high-risk nonmetastatic PCa patients. A 3-mo interval was chosen for practical and financial reasons. In addition, data indicated that ZA has a long bone retention time, with approximately 50% of the peak dose persisting there 240 d after administration, and pharmacokinetics demonstrating a multiphasic plasma disposition with an initial half-life of 0.2–1.4 h, followed by 39–4526 h for subsequent elimination, indicating that ZA levels may persist for 3 mo [12,13].

## 2. Materials and methods

### 2.1. Patients

From June 2004 to August 2007, 1433 patients were randomised. The main inclusion criteria were PCa with or without prior local curative prostatectomy or radiotherapy (no more than 6 mo between curative treatment and baseline) and a Karnofsky performance status ≥90. At least one of three high-risk factors had to be present: Gleason score 8–10, node-positive disease, or prostate-specific antigen (PSA) at diagnosis ≥20 ng/ml. The main exclusion criteria were visceral metastases or BMs, prior treatment with BPs, chemotherapy for PCa, antiandrogen monotherapy, and abnormal renal function (creatinine clearance [CCr] <30 ml/min). In 2005, after case reports of osteonecrosis of the jaw (ONJ) associated with BPs, an amendment was adopted to exclude patients with clinically significant active dental problems or planned jaw surgery [14].

### 2.2. Randomisation and treatment schedule

At randomisation, the minimisation method was used for treatment assignment described by Pocock [15], which provided approximate assignment equality for three predefined patient strata: centre, prior local treatment, and ADT. Patients were randomised into the zoledronic acid group (ZAG) receiving standard ADT, if applicable, plus ZA ($n$ = 716) and the control group (CG; $n$ = 717) receiving standard ADT only, if applicable. Patients receiving ADT at study entry could later stop ADT and patients not receiving ADT could later start ADT. The ZAG received a 15-min intravenous infusion of 4 mg ZA every 3 mo for ≤4 yr. The dose was reduced to 3.5 mg for patients with a CCr of 50–60 ml/min, 3.3 mg for 40–49 ml/min, and 3 mg for 30–39 ml/min. Supplemental Table 1 and Supplemental Figure 1 provide information on the administered ZA dose. All patients received concomitant therapy with 500 mg calcium and 400–500 IU vitamin D daily.

### 2.3. Study design and objectives

The primary objective was to evaluate the efficacy of ZA versus no ZA in terms of proportions of BMs at 4 ± 0.5 yr. On the assumption that 18% patients in the CG and 12% in the ZAG would develop BMs, 555 evaluable patients per group with a follow-up bone-imaging procedure (BIP) at 4 ± 0.5 yr would enable us to reject the null hypothesis that the proportions of patients with BMs between groups are equal with power of 0.80 and type 1 probability of 0.05 (uncorrected chi-square test). Anticipating a dropout rate of approximately 17%, 1300 randomised patients were needed. The secondary objectives were to evaluate the effects of ZA versus no ZA on reported adverse events (AEs), overall survival (OS), and time to BMs (ttBMs). After the study treatment phase of the last patient randomised, patients were followed for first BMs and/or OS for one additional year, resulting in a median study time of 4.8 yr.

### 2.4. Evaluation of bone metastases

BMs were assessed by local BIPs, mainly bone scans (BSs), in cases with pain or PSA >10 ng/ml. For patients with BS hot spots, additional imaging was recommended for metastases confirmation. After 4 yr, BIPs were recommended according to the study protocol. Supplemental Table 2 gives information on the number of BIPs. BIPs were centrally reviewed after blinding to clinical patient data with one of three possible outcomes: nonmetastatic, metastatic, or equivocal.

### 2.5. Adverse events

AE severity was graded according to the National Cancer Institute Common Toxicity Criteria v.3.

### 2.6. Ethics

All patients gave signed informed consent before participation. The study was approved by the institutional review board/independent ethics committee of the participating hospitals.

### 2.7. Statistical analysis

#### 2.7.1. Protocol-specific analyses

Categorical variables were reported as proportions with 95% confidence intervals (CIs). Continuous variables were reported as means plus or minus standard deviation. Differences in proportions and means were tested with the chi-square test and $t$ test, respectively. The Kaplan-Meier method and two-sided log-rank test were used to compare differences in OS and ttBMs between treatment arms. A multivariate Cox proportional-hazards analysis was used to assess the effect of variables on ttBMs. A two-sided $p$ value <0.05 was considered significant.

#### 2.7.2. Protocol nonspecific analyses

Because subgroups after curative treatment or receiving ADT may represent specific risk groups, differences in BM proportions in these

**Table 1 – Geographic distribution, patient demographics, and prognostic factors in the intention-to-treat population**

| | ZAG ($n$ = 694) | CG ($n$ = 699) | Total $n$ = 1393 |
|---|---|---|---|
| Country, *n* (%) | | | |
| Germany | 361 | 355 | 716 (51.4) |
| Denmark | 33 | 32 | 65 (4.7) |
| Finland | 42 | 41 | 83 (6.0) |
| Norway | 20 | 24 | 44 (3.2) |
| Sweden | 12 | 15 | 27 (1.9) |
| Belgium | 4 | 5 | 9 (0.7) |
| France | 40 | 39 | 79 (5.6) |
| Greece | 11 | 13 | 24 (1.7) |
| Italy | 55 | 63 | 118 (8.5) |
| Netherlands | 61 | 58 | 119 (8.5) |
| Spain | 33 | 36 | 69 (5.0) |
| Turkey | 14 | 11 | 25 (1.8) |
| Switzerland | 8 | 7 | 15 (1.1) |
| Race, *n* (%) | | | |
| White | 650 | 659 | 1309 (94.0) |
| Black | 2 | 0 | 2 (0.1) |
| Asian | 3 | 2 | 5 (0.4) |
| Other | 39 | 38 | 77 (5.5) |
| Age, yr | | | |
| Mean (SD) | 67 (8) | 67 (8) | 67 (8) |
| Range | 44–86 | 45–87 | 44–87 |
| Prior local treatment, *n* (%) | | | |
| No prior local treatment | 303 | 320 | 623 (44.7) |
| Prostatectomy | 322 | 311 | 633 (45.4) |
| Radiotherapy | 51 | 49 | 100 (7.2) |
| Prostatectomy and radiotherapy | 18 | 19 | 37 (2.7) |
| PSA category at diagnosis, *n* (%) | | | |
| PSA <20 ng/ml | 305 | 321 | 626 (44.9) |
| PSA ≥20 ng/ml | 389 | 378 | 767 (55.1) |
| PSA value, ng/ml, at diagnosis (SD) | 39.8 (70.0) | 40.2 (75.8) | 40.0 (72.9) |
| Minimum/maximum PSA values | 1.2/1177 | 1.6/1066 | 1.2/1177 |
| Time from diagnosis to study entry, wk (SD) | 18.7 (24.0) | 20.2 (42.0) | 19.5 (34.3) |
| Gleason score at diagnosis | | | |
| Gleason <8 | 267 | 259 | 526 (37.8) |
| Gleason ≥8 | 427 | 440 | 867 (62.2) |
| Nodal status at baseline | | | |
| N0 | 302 | 333 | 635 (45.6) |
| N1 | 181 | 152 | 333 (23.9) |
| Nx | 211 | 214 | 425 (30.5) |

CG = control group; PSA = prostate-specific antigen; SD = standard deviation; ZAG = zoledronic acid group.
Chi-square tests indicated no statistical significant differences between proportions in groups. The *t* test of means between groups indicated no significant differences.

subgroups were analysed separately with the chi-square test. Clinical patient data were explored to explain differences in the outcome of BIPs between the local and central reviewer. All statistical analyses were performed with SPSS v.20.0 (IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Effect of zoledronic acid on bone metastases and survival

In the ZAG and CG, 22 and 18 patients were excluded, leaving 694 and 699 patients, respectively, for ITT efficacy analysis (Fig. 1). Tables 1 and 2 show the patient demographics and ADT information. There were 1040 patients with BIP-BM outcome status at $4 \pm 0.5$ yr. The local urologist/radiologist diagnosed BMs in 88 of 515 patients (17.1%) in the ZAG and 89 of 525 patients (17.0%) in the CG (chi-square test: $p = 0.95$), with a difference between proportions of 0.1% (95% CI, −4.4 to 4.7) in favour of the CG. In 94 of 177 patients (53%), BS hot spots were confirmed as BMs with additional imaging. In the ITT population ($n = 1393$), the Kaplan-Meier estimated proportion of BMs after a median follow-up of 4.8 yr was 14.7% (95% CI, 11.8–17.5) in the ZAG versus 13.2% (95% CI, 10.4–16.0) in the CG (log-rank: $p = 0.65$; Fig. 2). In multivariate Cox proportional-hazards analysis, Gleason score, nodal status, and country were independent prognostic factors for ttBMs (Table 3). The impact of ZA on BMs in subgroups of patients with and without early ADT and prior local curative treatment revealed no significant differences between treatment groups (Tables 4 and 5).

Paired baseline and follow-up BIPs from 612 patients were subjected to central review. The central reviewer indicated that 12 of 612 patients had BMs at baseline, and these were excluded. Evidence of new BMs was seen in 36 of 280 patients (12.9%) in the ZAG and 34 of 320 patients (10.6%) in the CG (chi-square test: $p = 0.40$). There were more ZAG patients with an equivocal outcome at follow-up

**Table 2 – Use of androgen deprivation therapy in intention-to-treat population**

| ADT use | ZAG ($n$ = 694) | CG ($n$ = 699) |
|---|---|---|
| 1. Yes, used ADT prior to baseline | 354 patients | 362 patients |
| 2. Yes, started ADT at baseline within 6 wk after baseline | 76 patients | 80 patients |
| 3. No, patients started at least 6 wk after baseline | 53 patients | 58 patients |
| 4. No ADT throughout study | 211 patients | 199 patients |
| Group 1: Duration of ADT for patients with ADT prior to baseline, mo, mean (SD) | 2.0 (2.8) | 2.4 (7.6) |
| Groups 1–3: Total duration of ADT for patients during study calculated from baseline, mo, mean (SD) | 51.3 (23.5) | 51.7 (23.1) |
| Group 3: Duration of ADT for patients who started ADT at least 6 wk after baseline, mo, mean (SD) | 43.2 (20.9) | 49.0 (21.0) |

ADT = androgen-deprivation therapy; CG = control group; SD = standard deviation; ZAG = zoledronic acid group.
Chi-square tests indicated no statistical significant differences in proportions between groups. The $t$ test of means between groups indicated no significant differences.

BIP (chi-square test: $p = 0.02$; Supplemental Table 3). Survival data are presented in Table 6 and Figure 3.

### 3.2. Adverse events

For safety analysis, eight patients randomised for the CG who received ZA were evaluated in the ZAG. AEs were reported in 554 of 702 patients (78.9%) in the ZAG, and 512 of 691 patients (74.1%) in the CG (chi-square test: $p = 0.03$). There were 3130 AEs in the ZAG and 2649 in the CG (chi-square test: $p < 0.01$). The difference between groups could be attributed to the significantly greater numbers of general and musculoskeletal disorders in the ZAG. Typically, these AEs were influenza-like symptoms such as muscle/bone pain, arthralgia, fever, nausea, and dizziness, which were expected AEs of ZA. Most of the AEs were of limited severity: 1798 grade 1 (G1) and 833 G2 in the ZAG versus 1404 G1 and 757 G2 in the CG. There were 295 G3 and 113 G4 AEs in the ZAG versus 299 G3 and 117 G4 in the CG. Serious AEs were seen in 315 patients in the ZAG and 355 in the CG. Overall, 97 events in the ZAG led to withdrawal from the study compared with 16 in the CG, and 59 of 97 in the ZAG and 1 of 16 AEs in the CG were considered treatment related. Withdrawal for AEs in the ZAG was primarily caused by general and musculoskeletal disorders. Hypocalcaemia occurred in five patients (four in the ZAG and one in the CG). There were 10 patients with osteonecrosis (9 in the ZAG and 1 in the CG). One ZAG patient had femoral head

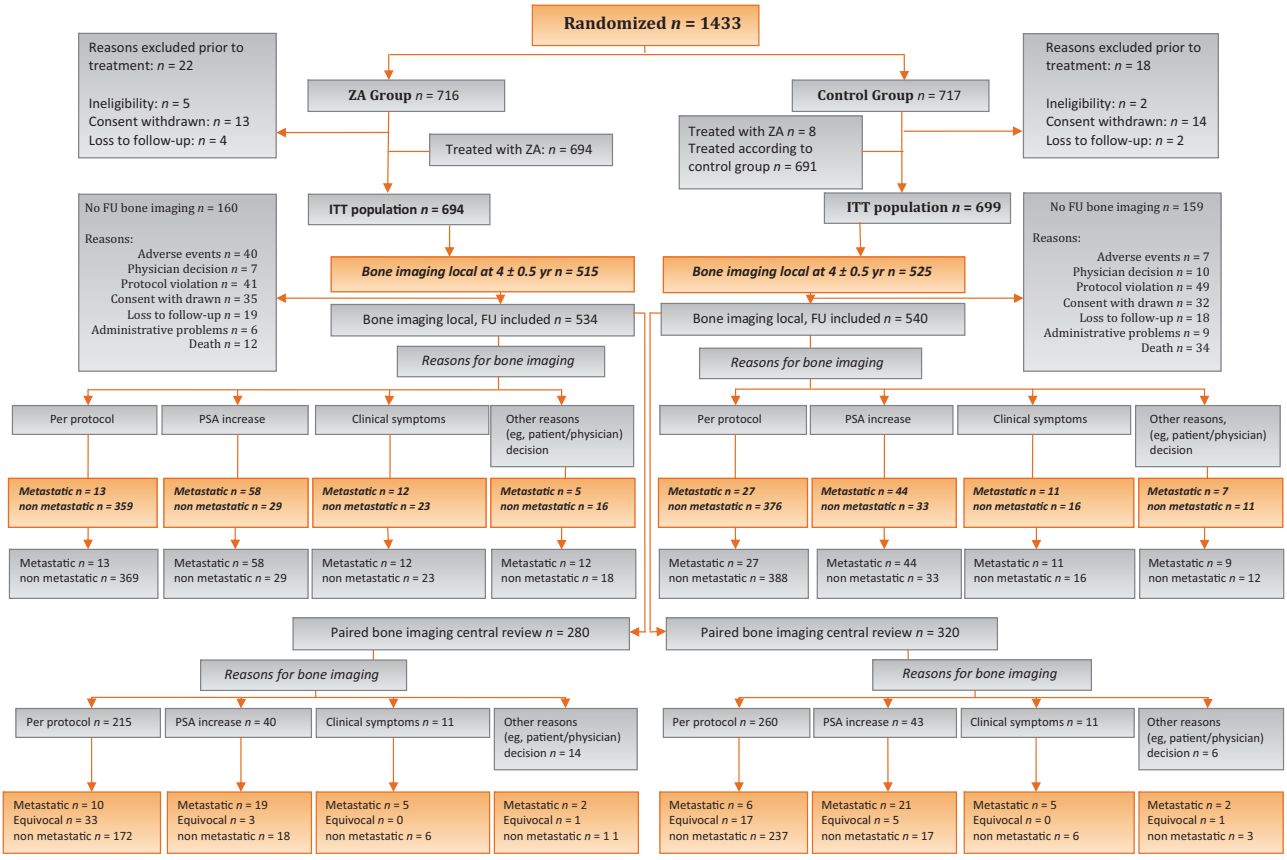



**Fig. 1 – Consolidated Standards of Reporting Trials.**
**FU = follow-up; ITT = intention to treat; PSA = prostate-specific antigen; ZA = zoledronic acid.**

**Table 3 – Multivariate Cox proportional-hazards analysis for time to bone metastases in intention-to-treat population ($n$ = 1393)**

| | | | 95% CI for HR | |
|---|---|---|---|---|
| | $p$ value | HR | Lower | Upper |
| Randomised treatment (reference: Control) | 0.62 | 1.075 | 0.806 | 1.435 |
| Country | | | | |
| Germany (reference) | **0.01** | | | |
| Denmark | 0.24 | 1.428 | 0.785 | 2.596 |
| Finland | 0.42 | 0.761 | 0.390 | 1.485 |
| Norway | **0.04** | **1.954*** | **1.046** | **3.653** |
| Sweden | **0.02** | **2.392*** | **1.140** | **5.020** |
| Belgium | 0.73 | 0.704 | 0.097 | 5.113 |
| France | 0.33 | 1.359 | 0.732 | 2.522 |
| Greece | 0.86 | 0.881 | 0.209 | 3.714 |
| Italy | 0.28 | 0.626 | 0.269 | 1.455 |
| Netherlands | **<0.01** | **2.266*** | **1.459** | **3.520** |
| Spain | 0.93 | 1.037 | 0.466 | 2.311 |
| Turkey | 0.60 | 0.584 | 0.080 | 4.289 |
| Switzerland | 0.19 | 2.192 | 0.682 | 7.039 |
| Prior local curative treatment (reference: no prior therapy) | 0.51 | 0.875 | 0.590 | 1.296 |
| ADT (reference: no ADT) | 0.06 | 1.525 | 0.988 | 2.355 |
| Gleason category (reference: <8) | **<0.01** | **2.139*** | **1.529** | **2.993** |
| PSA category (reference: <20 ng/ml) | 0.12 | 1.300 | 0.933 | 1.810 |
| Nodal status | | | | |
| N0 (reference) | **<0.01** | | | |
| N1 | **<0.01** | **2.158*** | **1.426** | **3.266** |
| Nx | **0.02** | **1.660*** | **1.079** | **2.552** |

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
* Bold HRs are statistically significant.

**Table 4 – Effect of androgen deprivation therapy (ADT) continued or started within 6 wk after randomisation versus no ADT on bone metastases**

| | ZAG, no. of patients (%; 95% CI) | CG. no. of patients (%; 95% CI) | Total no. of patients (%; 95% CI) | $p$ value chi-square test* |
|---|---|---|---|---|
| ADT | | | | |
| Metastasis | 72 (16.7; 13.3–20.6) | 72 (16.2; 13.0–20.1) | 144 (16.5; 14.1–19.1) | 0.86 |
| No metastasis | 358 (83.2; 79.4–86.7) | 370 (83.7; 79.9–86.7) | 728 (83.5; 80.8–85.9) | |
| Total | 430 | 442 | 872 | |
| No ADT | | | | |
| Metastasis | 23 (8.7; 5.6–12.8) | 19 (7.4; 4.5–11.3) | 42 (8.1; 5.9–10.7) | 0.58 |
| No metastasis | 241 (91.3; 87.2–94.4) | 238 (92.6; 88.7–95.5) | 479 (91.9; 89.3–94.1) | |
| Total | 264 | 257 | 521 | |

ADT = androgen deprivation therapy; CG = control group; CI = confidence interval; ZAG = zoledronic acid group.
* The $p$ value indicates comparison of proportions between study treatment arms of intention-to-treat subgroups with the chi-square test ($n$ = 1393).

**Table 5 – Effect of prior local curative treatment on bone metastases**

| | ZAG, no. of patients (%; 95% CI) | CG, no. of patients (%; 95% CI) | Total no. of patients (%; 95% CI) | $p$ value chi-square test* |
|---|---|---|---|---|
| Prior local curative Tx | | | | |
| Metastasis | 43 (11.0; 8.1–14.5) | 38 (10.0; 7.2–13.5) | 81 (10.5; 8.4–12.9) | 0.66 |
| No metastasis: total | 348 (89.0; 85.5–91.9) | 341 (90.0; 86.5–92.8) | 689 (89.5; 87.1–91.6) | |
| | 391 | 379 | 770 | |
| No prior local curative Tx | | | | |
| Metastasis | 52 (17.2; 13.1–21.9) | 53 (16.6; 12.7–21.1) | 105 (16.9; 14.0–20.0) | 0.84 |
| No metastasis: total | 251 (82.8; 78.1–86.9) | 267 (83.4; 78.9–87.3) | 518 (83.1; 80.0–86.0) | |
| | 303 | 320 | 623 | |

CG = control group; CI = confidence interval; Tx = therapy; ZAG = zoledronic acid group.
* The $p$ value indicates comparison of proportions between study treatment arms of intention-to-treat subgroups with the chi-square test ($n$ = 1393).

**Table 6 – Causes of death***

| | ZAG 694 patients | CG 699 patients |
|---|---|---|
| Prostate cancer related | 65 | 56 |
| Other causes (eg, cardiovascular, infection, trauma, or other cancer) | 39 | 57 |
| Unknown | 12 | 9 |
| Total | 116 | 122 |

CG = control group; ZAG = zoledronic acid group.
* No significant differences between ZAG and CG in intention-to-treat population (chi-square test for totals: $p = 0.71$).

osteonecrosis, which was not considered to be ZA related, and nine had ONJ. Eight patients with ONJ received a mean of ZA 40 mg (range: 28–63 mg).

## 4. Discussion

ZA has long-term benefits in patients with CRPC and BMs. It is approved for prevention of skeletal-related events in metastatic genitourinary cancers and recommended for routine use in CRPC according to the European Association of Urology guidelines [16]. ZA was the subject of a metastasis prevention trial in nonmetastatic CRCP patients that was closed early because the data safety monitoring board halted the study after accrual of 398 of 991 planned patients, since the event rate was lower than expected [17]. Oral clodronate trials showed improved OS in men with metastatic PCa starting ADT but no evidence of effect in men with nonmetastatic PCa [6]. Smith et al. demonstrated that denosumab significantly increased BM-free survival by a median of 4.2 mo compared with placebo and also significantly delayed ttBMs [18].

The additive anticancer effect of ZA combined with endocrine therapy in patients with early stage breast cancer was reported in the AZURE trial. Although the primary end point of disease-free survival was not met in the overall study population, subgroup analyses showed significant benefits for disease-free survival and OS in women ≥5 yr after menopause [19]. A significant anticancer effect of the addition of ZA on disease-free survival in premenopausal women with endocrine-responsive breast cancer taking anastrozole or tamoxifen was reported in the ABCSG-12 trial [20].

In our study there was no difference in the occurrence of BMs between treatment groups. At 4 yr, the local urologist/radiologist diagnosed BMs in 17.1% of the patients in the ZAG and 17.0% in the CG with a difference between proportions of 0.1% (95% CI, −4.4 to 4.7) in favour of the CG. When looking at the lower limit of the 95% CI, the difference in favour of ZA was 4.4% at the highest point, which was

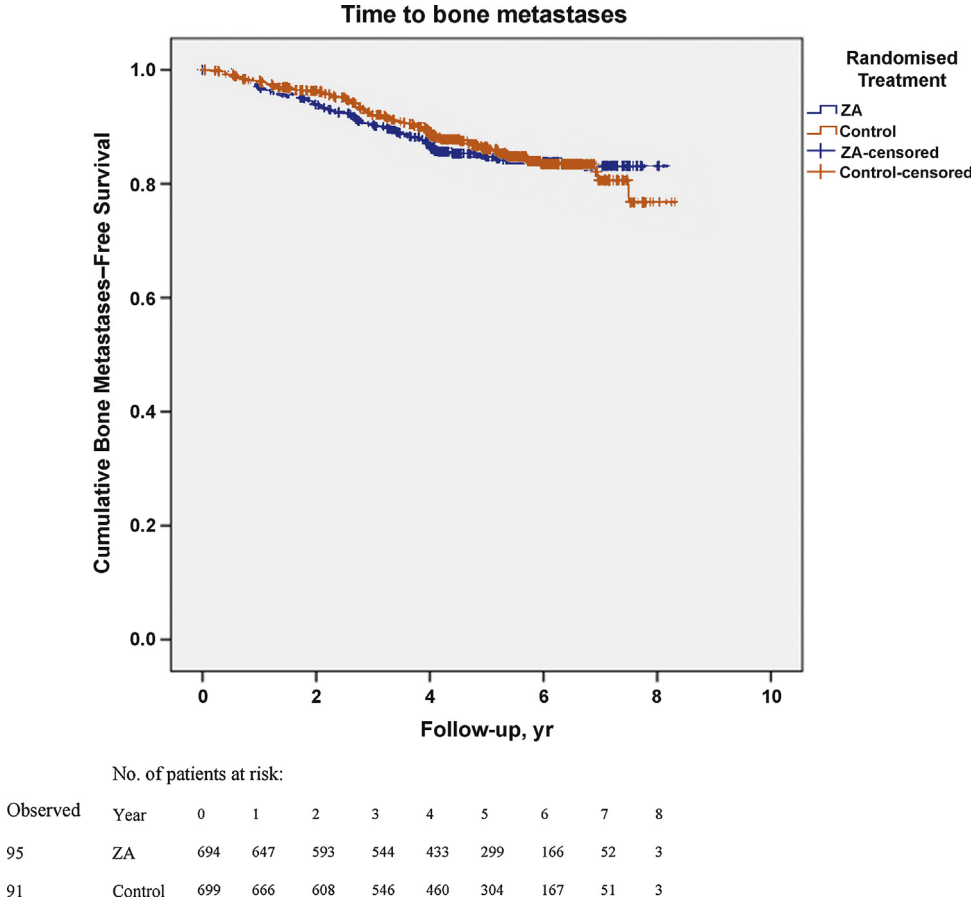
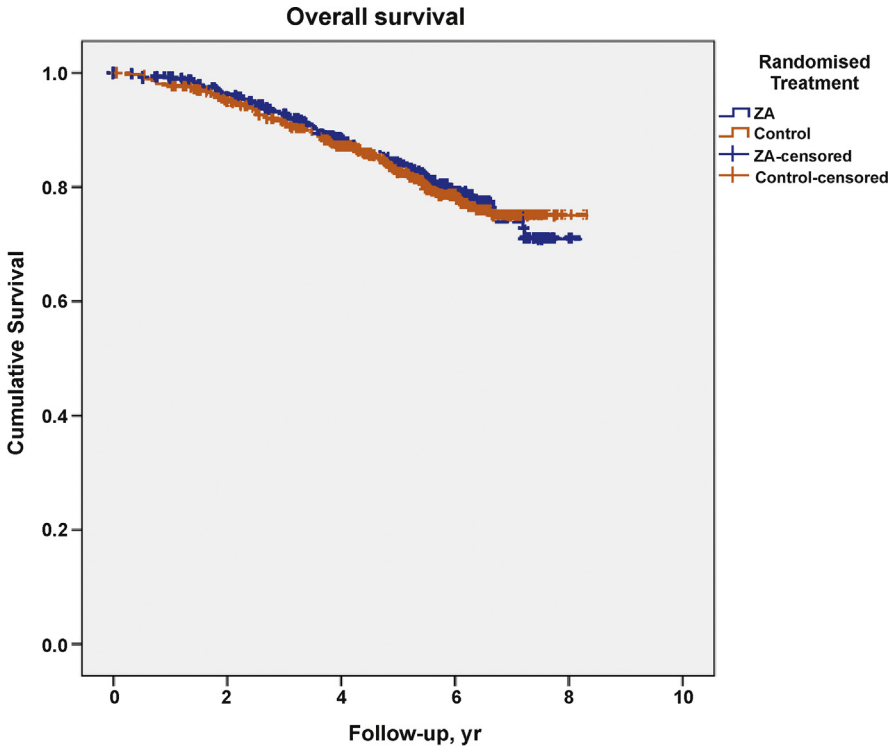



**Fig. 2 – Time to bone metastasis. No statistical significant differences between zoledronic acid (ZA) and control group in intention-to-treat population (log-rank: $p = 0.65$).**




No. of patients at risk:

| Observed | Year | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|---|
| 116 | ZA | 694 | 664 | 623 | 576 | 456 | 320 | 175 | 56 | 3 |
| 122 | Control | 699 | 677 | 623 | 575 | 485 | 325 | 172 | 54 | 3 |

**Fig. 3 – Overall survival. No statistical significant differences between zoledronic acid (ZA) and control group in intention-to-treat population (log-rank: $p = 0.76$).**

lower than the assumed difference of at least 6% used for sample size calculation. A maximum risk reduction of 4.4% is equivalent to treating 23 patients with ZA to prevent BMs in 1 patient at 4 yr. When taking into account the associated patient burden of treatment with ZA (eg, AEs, frequent visits to the hospital for intravenous infusions, costs), the potential benefit of ZA was insufficient and clinically irrelevant. The central review results led to similar conclusions. When specifically focussing on the subgroup receiving ADT as in the breast cancer trials, no differences could be detected. The ZA dosage may be important because in the AZURE trial, patients received more intense ZA treatment: 4 mg 3 to 4-weekly $\times$6, every 3 mo $\times$8, and every 6 mo $\times$5 thereafter [19]. In the ABCSG-12 trial, however, a less intense ZA administration schedule was used: 4 mg every 6 mo for 3 yr [20]. In our study, ZA was administered every 3 mo for $\leq$4 yr, suggesting that frequency of ZA administration may not be the only reason for failure to prevent BMs. However, the main mechanisms of the prevention of BMs by ZA in breast cancer may be different in PCa. If the BM-preventive effect of ZA in PCa is not exerted in the bone where sufficient drug levels are maintained up to 240 d but is based on its effect on the mevalonate pathway and the immune system (effects likely to be dose dependent), we cannot exclude the possibility that ZA could prevent BMs when used more intensively than the 3-mo regimen in our study [11–13,21]. The ZOOM trial data support this view because bone markers (N-terminal telopeptide) remained low in the patients treated monthly but increased in patients treated every 3 mo, suggesting that accumulation of ZA in the bone did not ensure extended bone turnover suppression [22].

BMs were assessed according to standard procedures where BSs were performed when symptoms appeared or PSA increased. BS hot spots are sensitive but not specific for metastases, and they are indistinguishable from other causes such as fractures or inflammation/infection without confirmative imaging. Unfortunately, only 53% of the patients with a positive BS had confirmative imaging, which reflects real-life practice patterns as a limitation of our study.

For a more accurate understanding of the number of BMs, the protocol was amended so that BIP images could be retrospectively collected for independent and blinded expert central review (F.L.). Participating centres were not originally selected based on their ability to generate BIP

images for central review. Consequently, we collected paired BIPs from only 612 patients, another study limitation. Remarkably, more patients in the ZAG had equivocal findings compared with the CG, specifically because PSA categories mainly showed incongruously low PSA levels. It was likely that ZA also affected bone, which was reflected in bone/muscle pain or arthralgia. Because most of the equivocal BIP results were derived from not-for-cause BIPs, it is unlikely that symptoms could explain the higher rate of equivocal BIP results in the ZAG.

Another limitation of our study was our heterogeneous population. Patients treated locally with curative intent had fewer BMs compared with those who were not. Similarly, patients receiving early ADT were potentially more prone to developing BMs.

Another possible limitation of our study was the open-label design resulting in patients in the ZAG attending clinic more frequently compared with the CG, which may have resulted in differential outcomes reporting. In our study, more AEs were reported in the ZAG, which may be biased by the more frequent visit schedule. However, according to the known side-effect profile of ZA, more AEs can be expected. A more frequent visit schedule could lead to more BIPs with more patients diagnosed as metastatic in the ZAG compared with the CG. As shown in Supplemental Table 2, the number of BIPs was comparable in both arms. Thus such a bias seems unlikely.

A multivariate Cox proportional-hazards analysis showed that geographic region was an independent risk factor for BMs. Patients in Sweden, Norway, and the Netherlands had double the likelihood to develop BMs compared with Germany. This equated with the effect of a Gleason score of 8–10 or node-positive disease. Although we may speculate that genetic or other high-risk factors (eg, a higher positive margin rate) could explain the differences in the occurrence of BMs between countries, the reasons for these findings are presently unclear.

A major AE of BPs is ONJ, which occurs in 1–7% of patients who have undergone dental extraction while receiving BPs [23,24]. The frequency of ONJ increased when more risk factors such as corticosteroids, radiotherapy, and chemotherapy were present. Dental extractions or poor dental hygiene are other prerequisites for ONJ development [14,23,24]. Once this information was published, these patients were excluded, and procedures to improve dental hygiene were recommended prior to ZA administration. After this amendment, no additional patients reported ONJ in our study.

## 5. Conclusions

From this multinational study in a nonmetastatic PCa population at high risk of BMs, ZA administered every 3 mo was demonstrated to be ineffective to prevent BMs at 4 yr.

***Author contributions:*** Wim P.J. Witjes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Other* (specify): None.

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## Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.02.014.

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