

# Influence of Delayed Zoledronic Acid Initiation on Disease-Free Survival in Postmenopausal Women With Endocrine Receptor-Positive Early Breast Cancer Receiving Adjuvant Letrozole: Exploratory Analyses From the ZO-FAST Trial

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## ABSTRACT

**Introduction:** Bisphosphonates (BPs) combined with adjuvant endocrine therapy have been shown to prevent aromatase inhibitor-associated bone loss (AIBL) and improve outcomes in recent clinical trials in patients with hormone receptor-positive (HR+) early breast cancer (EBC). Accelerated bone turnover (a common phenomenon during AIBL) has been associated with increased risk of bone metastasis in EBC (Lipton A, et al. St. Gallen 2009, Abstract 244), but little is known about the effect of BPs on the disease course in women with EBC and progressing AIBL. We have previously demonstrated that adding ZOL to adjuvant therapy significantly improved bone mineral density (BMD) and prolonged disease-free survival (DFS) vs delayed ZOL (de Boer R, et al. SABCS 2010, Poster P5-11-01). We report here the prognostic factors for DFS and the effect of ZOL initiation in the delayed ZOL (DZOL) arm of the ZO-FAST trial at 5 years' median follow-up.

**Methods:** The ZO-FAST trial randomised postmenopausal women with HR+ EBC initiating letrozole (LET; 2.5 mg qd x 5 years) with a BMD T-score  $\geq -2$  (N = 1,065) to immediate (IMZOL; 4 mg q 6 months) or DZOL (initiated for post-baseline T-score  $< -2$ , or nontraumatic/asymptomatic fractures). The primary endpoint was change in BMD at 12 months; patients were followed for disease recurrence and overall survival for 5 years (secondary endpoints). Exploratory Cox regression analyses were performed to identify prognostic factors for DFS in the DZOL arm.

**Results:** At 60 months' follow-up, IMZOL significantly reduced the risk of a DFS event by 34% vs DZOL (42 vs 62 events; ~80% distant recurrences and 20% local; hazard ratio [HR] = 0.66; 95% confidence interval [CI], 0.44-0.97;  $P = .034$ ) in the intent-to-treat population (N = 1,065; n = 532 IMZOL; n = 533 DZOL). In exploratory analyses of the DZOL arm (n = 535; safety population), patients who initiated DZOL treatment (n = 144) had significantly improved DFS (10 events; HR = 0.462; 95% CI, 0.23-0.94;  $P = .033$ ) compared with DZOL-arm patients who never initiated ZOL (53 events; n = 391). Other significant prognostic factors for DFS events in the DZOL arm were age  $\geq 65$  years at study entry (HR = 1.949; 95% CI, 1.09-3.47;  $P = .024$  vs age  $< 65$  years) and cancer T-stage  $\geq 2$  (HR = 2.155; 95% CI, 1.03-4.51;  $P = .042$  vs T-stage  $< 2$ ).

**Conclusion:** Exploratory analyses of the ZO-FAST database revealed significant DFS benefits from initiation of ZOL treatment for post-baseline fractures or T-scores  $< -2$ , suggesting that ZOL (even if initiated late) can positively influence the disease course in patients with AIBL. Together with other studies showing DFS benefits from ZOL in patients with complete ovarian suppression/postmenopausal status (Coleman RE, et al. *N Engl J Med*. 2011;365:1306-1405; Gnani M, et al. *N Engl J Med*. 2009;360:679-691), these data suggest that treating (and ideally, preventing) AIBL may also improve DFS in patients with HR+ EBC.

## INTRODUCTION

- Aromatase inhibitor (AI) treatment is the standard of care for postmenopausal women with hormone-receptor-positive breast cancer (BC)<sup>1-3</sup>
- Treatment with AIs in women who are already postmenopausal further reduces circulating oestrogen to undetectable levels,<sup>4</sup> and exacerbates bone loss
  - In addition to accelerated bone loss,  $\downarrow$  oestrogen levels are associated with  $\uparrow$  bone turnover, which has been associated with increased risk of bone metastasis in early BC<sup>5</sup>
- Bisphosphonates (BPs) such as zoledronic acid (ZOL) can inhibit osteoclast-mediated bone resorption and help maintain bone mineral density (BMD) in postmenopausal women<sup>6,7</sup>
  - BPs initiated concurrently with adjuvant endocrine therapy have been shown to prevent AI-associated bone loss (AIBL)
- Both preclinical and clinical studies suggest that BPs may provide potential anticancer benefits in addition to their established bone-protective activities<sup>8-13</sup>
  - ZOL, in particular, has demonstrated promising anticancer activity in several clinical studies, including women receiving ovarian suppression and adjuvant endocrine therapy for early BC and in postmenopausal patients receiving adjuvant chemotherapy<sup>14,15</sup>
- We have previously demonstrated that adding ZOL to adjuvant therapy significantly  $\uparrow$  BMD and  $\uparrow$  DFS versus delayed ZOL (DZOL)<sup>16</sup>
  - However, little is known about the effects of BPs on the disease course in women with early BC and progressing AIBL
- We report here the prognostic factors for DFS and the effect of ZOL initiation in the DZOL arm of the ZO-FAST trial at 5 years' median follow-up (Clinical Trials Registration Number: NCT00171340)

## METHODS

### Patients

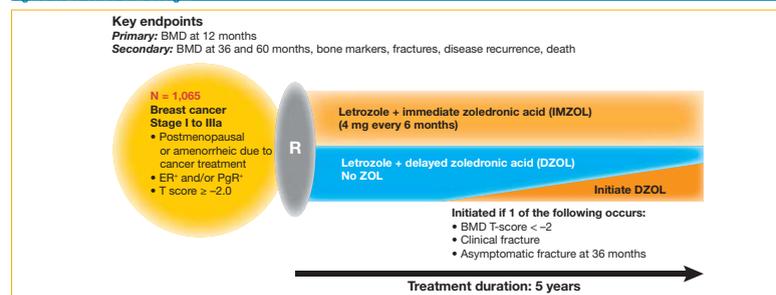
- Inclusion Criteria**
- Postmenopausal women with oestrogen-receptor-positive and/or progesterone-receptor-positive stage I, II, or IIIA early BC
  - Baseline Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$
  - Baseline lumbar spine (LS) and total hip (TH) T-score  $\geq -2.0$
  - Surgical resection completed; chemotherapy followed by radiation therapy  $\leq 12$  weeks prior without evidence of residual disease
- Exclusion Criteria**
- Clinical or radiologic evidence of distant metastases
  - Existing LS or hip fracture or a history of low-intensity fractures
  - Renal dysfunction, other malignancies, or diseases known to affect bone density
  - Prior treatment with letrozole (LET) or other adjuvant hormone therapy, endocrine therapy of any type, intravenous BPs within the past 12 months, or prolonged treatment with drugs that affect the skeleton

### Study Details

- Open-label, multicentre, randomised phase III study
  - BMD assessments using standardised, cross-calibrated dual-energy x-ray absorptiometry (DEXA) equipment, with central review
- Treatment (Figure 1)
  - All patients received adjuvant oral daily LET for 5 years and were randomised to receive either immediate ZOL (IMZOL) or DZOL treatment
  - Stratification factors: Adjuvant chemotherapy, baseline T-score, and stage of menopause
  - All patients also received calcium and vitamin D supplements

## METHODS (continued)

Figure 1. ZO-FAST trial design.



The shaded area in the DZOL arm represents on-study initiation of ZOL for post-baseline BMD decreases or fractures. Abbreviations: BC, breast cancer; BMD, bone mineral density; ER, oestrogen receptor; PgR, progesterone receptor; R, randomisation.

- Endpoints
  - Primary: Percentage change in LS (L2-L4) BMD at 12 months in the IMZOL and DZOL treatment arms
  - Secondary: LS BMD assessments at 24, 36, 48, and 60 months; percentage change in TH BMD at each assessment; incidence of fractures over 3 years; time to disease recurrence; OS; safety

### Statistical Methods

- All statistical tests were performed using a 2-sided significance level of  $P = .05$
- DFS was defined as time to disease recurrence (local, regional, or distant BC recurrence) or death from any cause
- Kaplan-Meier estimates of event-free proportions and the associated 95% confidence intervals (CIs) were calculated for DFS and OS in each treatment arm at annual intervals
- Log-rank tests and hazard ratios (both stratified by prior adjuvant chemotherapy, BMD T-score, and menopausal status) were used to compare the 2 treatment arms

### Exploratory Analyses

- Exploratory Cox regression analyses were performed to identify prognostic factors for DFS in the DZOL arm

## RESULTS

### Patients

- 1,065 patients from 132 centres across 28 countries were randomised to the 2 treatment arms
- Baseline demographics and patient disposition at 60 months were similar between the treatment groups<sup>14</sup>
  - Patients in both groups were treated with LET for a median of ~60 months (range, 0 to 67.8 months)
  - A median of 11 infusions of ZOL were administered to patients in the IMZOL group

### Efficacy Analyses

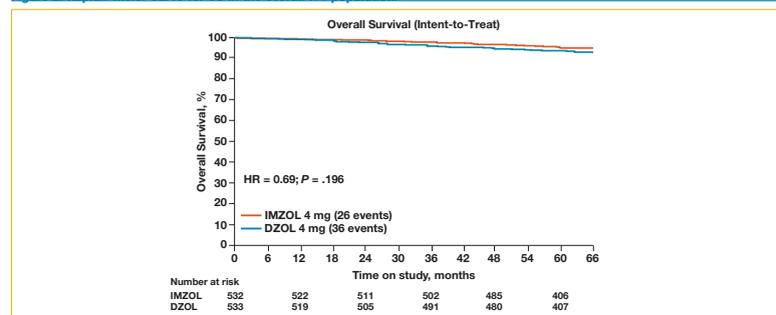
#### Bone Mineral Density

- At 60 months, mean change in LS BMD was +4.3% in the IMZOL group and -5.4% in the DZOL group ( $P < .0001$ )
- Mean change in TH BMD was +1.6% with IMZOL and -4.2% with DZOL ( $P < .0001$ )

#### Overall Survival

- At 60 months' follow-up, OS was not significantly different between groups (hazard ratio [HR] = 0.69; 95% CI = 0.42, 1.14;  $P = .196$ ) in the intent-to-treat (ITT) population (N = 1,065; n = 532 IMZOL; n = 533 DZOL; Figure 2)

Figure 2. Kaplan-Meier curve for OS in the overall ITT population.



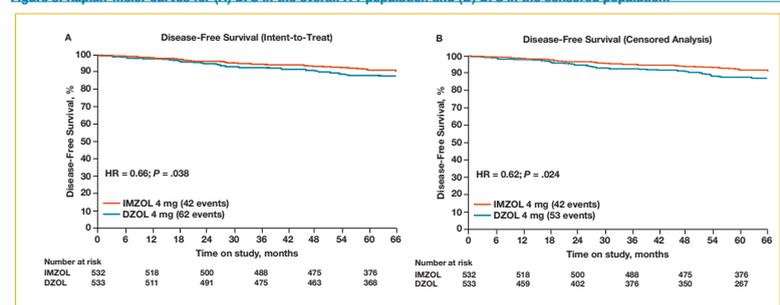
Abbreviations: DZOL, delayed ZOL; HR, hazard ratio; IMZOL, immediate ZOL; ITT, intent-to-treat; OS, overall survival; ZOL, zoledronic acid.

## RESULTS (continued)

### Disease-Free Survival

- At 60 months' follow-up, IMZOL significantly reduced the risk of a DFS event by 34% versus DZOL in the ITT population (N = 1,065; n = 532 IMZOL; n = 533 DZOL; Figure 3A)
  - 42 versus 62 events; HR = 0.66; 95% CI = 0.44, 0.97;  $P = .038$  (unstratified)
  - ~80% distant recurrences and 20% local recurrences
- In analyses censoring patients who initiated ZOL in the DZOL arm, IMZOL significantly improved DFS versus patients who never received ZOL (HR = 0.62;  $P = .024$ ; Figure 3B)
  - Because of the ZO-FAST trial design, censored analyses may provide a more accurate portrayal of the effect of ZOL versus no ZOL on DFS than the ITT population

Figure 3. Kaplan-Meier curves for (A) DFS in the overall ITT population and (B) DFS in the censored population.



Abbreviations: DFS, disease-free survival; DZOL, delayed ZOL; HR, hazard ratio; IMZOL, immediate ZOL; ITT, intent-to-treat; ZOL, zoledronic acid.

### Exploratory Analyses of DFS in the DZOL Arm

- 144 patients (26.9%) in the DZOL group had initiated ZOL treatment after a median of 12.8 months for post-baseline decreases in BMD or for fractures, per the protocol definition
- A larger proportion of patients in the DZOL arm with baseline osteopenia initiated ZOL therapy on-study compared with patients with normal baseline BMD (Table 2)
  - ZOL was initiated in the DZOL group in 81 of 165 patients (49%) with baseline osteopenia ( $-2.0 \leq$  T-score  $< -1.0$ ) and in 63 of 370 of patients (17%) with normal baseline BMD (T-score  $> -1.0$ )
- Other baseline characteristics and known prognostic factors were generally balanced between patients in the DZOL arm who initiated ZOL and those who never received ZOL

Table 1. Patient Demographics and Baseline Disease Characteristics (DZOL Arm—Safety Population)

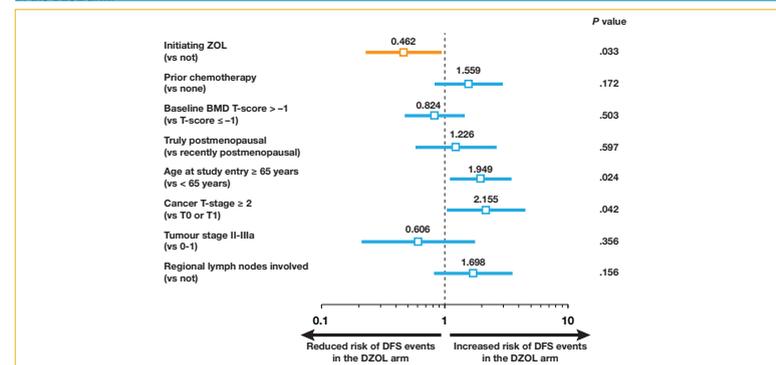
Characteristic	DZOL—Treated (n = 144)	DZOL—Not Treated (n = 391)
Median age, years (range)	57 (45 - 78)	58 (37 - 81)
Median body mass index, kg/cm <sup>2</sup> (range)	25.7 (16.7 - 43.3)	27.1 (18.6 - 65.8)
ECOG PS, n (%)		
0	125 (86.8)	356 (91.0)
1	18 (12.5)	30 (7.7)
2	1 (0.7)	3 (0.8)
Unknown	0	2 (0.5)
Stratification factors, n (%)		
Adjuvant chemotherapy		
No adjuvant chemotherapy	63 (43.8)	187 (47.8)
Prior adjuvant chemotherapy	81 (56.3)	204 (52.2)
Menopausal status		
Recently menopausal	21 (14.6)	69 (17.6)
Truly postmenopausal	123 (85.4)	322 (82.4)
T-score*		
T-score between -2.0 and -1.0 SD	81 (56.3)	84 (21.5)
T-score $> -1.0$ SD	63 (43.8)	307 (78.5)

\*T-scores were substantially different between patients who initiated delayed ZOL treatment versus those who did not. Abbreviations: DZOL, delayed ZOL; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; ZOL, zoledronic acid.

## RESULTS (continued)

- Exploratory analyses of the DZOL arm (n = 535; safety population) identified 3 factors independently associated with DFS (Figure 4)
  - Initiating DZOL treatment (n = 144) significantly  $\uparrow$  DFS (9 events; HR = 0.46; 95% CI = 0.23, 0.94;  $P = .033$ ) versus untreated patients in the DZOL arm (ie, patients who never initiated ZOL; 53 events; n = 391)
  - Tumour stage at study entry (HR = 2.16;  $P = .042$  for  $\geq$  T2 versus T0 or T1)
  - Age at study entry (HR = 1.95;  $P = .024$  for age  $\geq 65$  versus  $< 65$  years)

Figure 4. Forest plot of factors examined in exploratory Cox regression analyses to identify prognostic factors for DFS in the DZOL arm.



Abbreviations: BMD, bone mineral density; CI, confidence interval; DFS, disease-free survival; DZOL, delayed ZOL; ZOL, zoledronic acid.

### Safety

- Number of patients with fractures (39 IMZOL vs 38 DZOL) or atrial fibrillation (2 IMZOL vs 6 DZOL) were statistically similar in the IMZOL versus DZOL arms, and no effects on cholesterol levels were detected
  - Few patients experienced pathologic fractures (0 IMZOL vs 1 DZOL) and spinal cord compression (1 IMZOL vs 4 DZOL)
- Renal AEs were similar between treatment arms
  - 10 AEs in the IMZOL arm
  - 6 AEs in the DZOL arm
- 9 potential osteonecrosis of the jaw (ONJ) events from 7 patients were reported
  - Each event was independently adjudicated by an external panel
  - ONJ was confirmed for 3 events, deemed possible (insufficient data) for 2 events, and excluded for the remaining 4 events
- Pyrexia was reported in 80 of 525 evaluable patients (15.2%) in the IMZOL arm and in 19 of 535 evaluable patients (3.6%) in the DZOL arm

## CONCLUSIONS

- Exploratory analyses of the ZO-FAST database revealed significant DFS benefits from initiation of ZOL treatment for post-baseline fractures or T-scores  $< -2.0$ 
  - Suggests that ZOL (even if initiated late for progressing AIBL) can positively influence the disease course in patients receiving endocrine therapy for early BC
- Data support other studies showing DFS benefits with ZOL in patients with complete ovarian suppression/postmenopausal status<sup>10,15</sup>
  - These data suggest that treating (and ideally, preventing) AIBL also may improve DFS in patients with hormone-receptor-positive early BC

### References

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