ZOOM: A Prospective, Randomized Trial of Zoledronic Acid for Long-term Treatment in Patients With Bone-Metastatic Breast Cancer After 1 Year of Standard Zoledronic Acid Treatment


On behalf of ZOOM Investigators

Ripamonti C, et al. ASCO 2012 (Abstract 9005)
Disclosure Information
Relationships Relevant to This Session

• Study supported by funding from Novartis
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Ripamonti, Carla
No relevant relationships to disclose.

Please note: all disclosures are reported as submitted to ASCO, and are always available at chicago2012.asco.org

Ripamonti C, et al. ASCO 2012 (Abstract 9005)
Background

• Pivotal trials demonstrated the efficacy of ZOL (4 mg q 4 wk) for reducing the risk of SREs for up to 2 years of treatment in patients with bone metastases from BC

• International guidelines recommend treatment with BPs until there is evidence of substantial decrease in performance status to reduce SRE risk in patients with bone metastases from BC

• A less frequent regimen of ZOL after 1 year of treatment at the standard dosing schedule might contribute to improved patient compliance and safety, and help reduce cost while maintaining efficacy

Abbreviations: BC, breast cancer; q, every; SRE, skeletal-related event; ZOL, zoledronic acid.

ZOOM Study Design

Endpoints:

**Primary:** Skeletal morbidity rate (SMR)

**Secondary:** Proportion of patients experiencing SREs (overall and by event), time to first SRE, SMR by event, bone pain, use of analgesics, bone marker levels, safety

**Key eligibility criteria**
- BC stage IV
- Confirmed bone metastasis
- Prior zoledronic acid treatment (4 mg q 4 wk) × 9-12 infusions

**N = 420 (Planned)**

**Arm 1:** Zoledronic acid (4 mg q 12 wk)

**Arm 2:** Zoledronic acid (4 mg q 4 wk)

**Treatment duration 1 year**

**Accrual:** February 2006 - February 2010

Abbreviations: q, every; R, randomization; SRE, skeletal-related event.
Statistical Analysis

• Primary endpoint (SMR) evaluated in terms of non-inferiority
  – 12-week dosing non-inferior to 4-week dosing if the upper limit of the CI is ≤ predefined non-inferiority margin of 0.56 based on historical SMR data
  – 95% CI calculated using estimate of variability and least squares means from ANCOVA (study duration as a covariate)

• Sample size to detect non-inferiority with 80% power was 420 patients

Non-inferiority margin recalculated to 0.19 (considering that the observed variability was much lower [1/3] than the assumed variability. All other elements of sample size calculation remained consistent with the original plan).

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; SMR, skeletal morbidity rate; SRE, skeletal-related event.
Patient Disposition

Screened: N = 430

Randomized: N = 425

ZOL q 12 wk: n = 209
Completed: 149 (71%)
Discontinued: 60 (29%)
  - Adverse events: 21 (10%)
  - Other: 14 (7%)
  - Death: 11 (5%)
  - Protocol violations: 10 (5%)
  - Unsatisfactory effect: 4 (2%)

ZOL q 4 wk: n = 216
Completed: 142 (66%)
Discontinued: 74 (34%)
  - Adverse events: 27 (13%)
  - Other: 25 (12%)
  - Death: 10 (5%)
  - Protocol violations: 8 (4%)
  - Unsatisfactory effect: 4 (2%)
## Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ZOL q 12 wk (Arm 1)</th>
<th>ZOL q 4 wk (Arm 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 209 (%)</td>
<td>n = 216 (%)</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>60 (12)</td>
<td>60 (12)</td>
</tr>
<tr>
<td>Race—Caucasian</td>
<td>209 (100)</td>
<td>216 (100)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>207 (99)</td>
<td>214 (99)</td>
</tr>
<tr>
<td>2</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Time from diagnosis to study entry, mo, mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic BC</td>
<td>23.5 ± 25.0</td>
<td>22.6 ± 26.0</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>18.1 ± 19.7</td>
<td>16.7 ± 18.7</td>
</tr>
<tr>
<td>Prior SREs</td>
<td>120 (57)</td>
<td>124 (57)</td>
</tr>
<tr>
<td>BPI score, 0-10, mean ± SD</td>
<td>2.0 ± 1.8</td>
<td>2.1 ± 1.9</td>
</tr>
<tr>
<td>Analgesic use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>131 (63)</td>
<td>138 (64)</td>
</tr>
<tr>
<td>Mild/strong opioids</td>
<td>32 (15)</td>
<td>45 (21)</td>
</tr>
<tr>
<td>General oral health condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>165 (79)</td>
<td>180 (84)</td>
</tr>
<tr>
<td>Excellent</td>
<td>22 (11)</td>
<td>20 (9)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BC, breast cancer; BPI, brief pain inventory; ECOG, Eastern Cooperative Oncology Group; mo, months; q, every; SD, standard deviation; SRE, skeletal-related event; ZOL, zoledronic acid.
### Primary Efficacy Analysis—SMR

<table>
<thead>
<tr>
<th></th>
<th>ZOL q 12 wk (Arm 1)</th>
<th>ZOL q 4 wk (Arm 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (ITT population)</td>
<td>209</td>
<td>216</td>
</tr>
<tr>
<td>Mean SMR (95% CI)</td>
<td>0.26 (0.15, 0.37)</td>
<td>0.22 (0.14, 0.29)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.09 to 0.17</td>
<td></td>
</tr>
</tbody>
</table>

The upper limit of the CI (0.17) was less than the recalculated non-inferiority margin of 0.19. This result indicates that the efficacy of the q 12 wk arm was not inferior to the q 4 wk arm.

*Abbreviations: CI, confidence interval; ITT, intent to treat; LS, least squares; q, every; SMR, skeletal morbidity rate; ZOL, zoledronic acid.*
## Secondary Efficacy Analyses—Proportion of Patients With an On-Study SRE

<table>
<thead>
<tr>
<th>Protocol-Defined SRE Types</th>
<th>Patients, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZOL q 12 wk (Arm 1) n = 209</td>
<td>ZOL q 4 wk (Arm 2) n = 216</td>
<td></td>
</tr>
<tr>
<td>Any SRE</td>
<td>14.8</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>10.5</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Pathologic fracture (nonvertebral)</td>
<td>3.4</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Pathologic fracture (vertebral)</td>
<td>1.4</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia of malignancy</td>
<td>0.5</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: q, every; SRE, skeletal-related event; ZOL, zoledronic acid.
Exploratory Analyses of NTX Levels

• NTX levels (baseline and q 3 mo on-study) were assessed in a subset of 220 patients

• Similar median baseline serum NTX levels
  – ZOL q 12 wk: 9.55 nmol/L
    • Interquartile range: 7.60 to 12.30 nmol/L
  – ZOL q 4 wk: 9.60 nmol/L
    • Interquartile range: 8.00 to 12.30 nmol/L

Abbreviations: Cr, creatinine; NTX, N-telopeptide of type I collagen; q, every; ZOL, zoledronic acid.
Change in NTX Levels On-Study

Abbreviations: NTX, N-telopeptide of type I collagen; q, every; ZOL, zoledronic acid.

*P < .05 by Wilcoxon test comparing arms
## Safety—AEs and Serious AEs

<table>
<thead>
<tr>
<th>AE (preferred term)</th>
<th>ZOL q 12 wk (Arm 1) n = 209 (%)</th>
<th>ZOL q 4 wk (Arm 2) n = 216 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>159 (76)</td>
<td>184 (85)</td>
</tr>
<tr>
<td><strong>Selected AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute-phase reaction related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22 (11)</td>
<td>28 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (5)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (7)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Renal/urinary AEs</td>
<td>9 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0 (0)</td>
<td>1 (&lt; 1)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5 (2)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Total SAEs</td>
<td>21 (10)</td>
<td>29 (13)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 (2)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; q, every; ZOL, zoledronic acid; SAE, serious adverse event.

<sup>a</sup> The event of acute renal failure was considered to be grade 1 in severity and not serious.  
<sup>b</sup> All ONJ cases were reported as an SAE.
ZOOM: Study Limitations

• Open-label design
• Different clinic visit frequencies between arms (thus assessment of adverse events)
• No prespecified imaging frequency
• Single-country study
ZOOM: Summary

• ZOOM is the first trial to compare quarterly vs monthly ZOL in BC patients after ~1 y of standard ZOL therapy

• Primary endpoint of SMR was met: q 12 wk ZOL was non-inferior to q 4 wk ZOL

• Safety profiles of the 2 treatment schedules were similar
  – No meaningful differences in renal AEs or ONJ event rates

• Exploratory analyses of median NTX levels showed an increase from baseline in the q 12 wk arm, but almost no change in the q 4 wk arm

Abbreviations: AE, adverse event; BC, breast cancer; NTX, N-telopeptide of type I collagen; ONJ, osteonecrosis of the jaw; q, every; SMR, skeletal morbidity rate; ZOL, zoledronic acid.
ZOOM: Points To Consider

• Low incidence of SREs in the trial support the efficacy of standard ZOL dosing (4 mg q 4 wk) for 1 year initiated at the time of diagnosis of bone metastasis

• The differences observed in median NTX levels between ZOL q 12 wk and ZOL q 4 wk suggest that longer follow-up is needed to assess whether ZOL q 12 wk can maintain adequate efficacy on SREs over time

• Ongoing studies with a similar design to ZOOM (eg, OPTIMIZE-2) may further elucidate outcomes with reduced-frequency ZOL dosing after at least 1 year of standard therapy

Abbreviations: NTX, N-telopeptide of type I collagen; ONJ, osteonecrosis of the jaw; q, every; SRE, skeletal-related event; ZOL, zoledronic acid.

OPTIMIZE-2: Phase 3 Randomized Double-blind Multicenter Trial

- **Primary endpoint**: Proportion of patients with at least 1 SRE on study (non-inferiority)
- **Secondary endpoints**: Time to first SRE, bone pain on study, bone marker levels (NTX, BSAP)

**N = 423 (Planned)**
- BC stage IV
  - Confirmed bone metastasis
  - Prior intravenous bisphosphonate treatment for ≥ 1 year (≥ 9 doses during the first 10-15 months of treatment)

**Arm 1:** Zoledronic acid (4 mg q 12 wk)

**Arm 2:** Zoledronic acid (4 mg q 4 wk)

Treatment duration 12 mo
Monthly safety and efficacy assessments

Abbreviations: BC, breast cancer; BSAP, bone-specific alkaline phosphatase; NTX, N-telopeptide of type I collagen; q, every; R, randomization; SRE, skeletal-related event.

Acknowledgments

• The patients who participated in and contributed to this trial

• The ZOOM study investigators

• The investigators who participated in the writing committee