Bisphosphonates in Breast Cancer: From Prevention of Bone Loss to Prevention of Recurrence

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Associate Chief, Hematology/Oncology
Director, Breast Cancer Program
University of Pittsburgh
Aromatase Inhibitors Are Consistently Superior to Tamoxifen (Disease-Free Survival)

<table>
<thead>
<tr>
<th>Trial (months)</th>
<th>Aromatase inhibitor</th>
<th>Absolute benefit, %</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC (68)¹</td>
<td>Anastrozole up front (5 yr)</td>
<td>2.5</td>
<td>0.83</td>
</tr>
<tr>
<td>BIG 1-98 (26)²</td>
<td>Letrozole up front (5 yr)</td>
<td>2.6</td>
<td>0.81</td>
</tr>
<tr>
<td>BIG 1-98 (51)³*</td>
<td>Letrozole up front (5 yr)</td>
<td>2.9</td>
<td>0.82</td>
</tr>
<tr>
<td>IES (30)⁴</td>
<td>Exemestane (3 yr)</td>
<td>4.7</td>
<td>0.68</td>
</tr>
<tr>
<td>IES (56)⁵</td>
<td>Exemestane (5 yr)</td>
<td>3.4</td>
<td>0.76</td>
</tr>
<tr>
<td>ARNO/ABCSG (28)⁶</td>
<td>Anastrozole (2 yr)</td>
<td>3.1</td>
<td>0.60</td>
</tr>
<tr>
<td>MA-17 (30)⁷</td>
<td>Letrozole (5 yr) vs placebo</td>
<td>4.9</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Analysis restricted to monotherapy arm A vs arm B.

MA.17 Post-Unblinding Cohorts

Median F/U
30 Months 54 (16 – 86) Months

Tamoxifen n = 5187

Placebo n = 2594

Letrozole (LET) n = 2457

No Letrozole (PLAC) n = 613

Letrozole (PLAC-LET) n = 1655

1998 2003 2005

Unblinding

Ingle et al  Goss et al

SABCS 2005
Percentage of Patients with Recurrence

SABCS 2005
Adverse Events After Unblinding

- Bone Fracture: P=0.60
- New Osteoporosis: P=0.007
- CV Disease: P=0.84

SABCS 2005
ATAC trial design

Postmenopausal women with invasive breast cancer (n = 9366)

Surgery ± radiotherapy ± chemotherapy

Randomisation 1:1:1 for 5 years

Anastrozole (n = 3125)

- ITT population n = 3125
- Safety population n = 3092
- HR+ subpopulation n = 2618

Tamoxifen (n = 3116)

- ITT population n = 3116
- Safety population n = 3094
- HR+ subpopulation n = 2598

Discontinued following initial analysis as no efficacy or tolerability benefit compared with tamoxifen arm

ITT, intent-to-treat; HR+, hormone receptor-positive
Disease-free survival
HR+ patients

<table>
<thead>
<tr>
<th>Follow-up time (years)</th>
<th>Patients</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tbody>
</table>

At risk:
A  2618  2541  2453  2361  2278  2159  1995  1801  1492  608
T  2598  2516  2400  2306  2196  2075  1896  1711  1396  547

HR, hazard ratio; CI, confidence interval
# All AIs Significantly Reduce Estrogen Levels

<table>
<thead>
<tr>
<th>AI drug</th>
<th>Aromatase inhibition, %</th>
<th>Plasma estradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole¹</td>
<td>&gt; 99.1</td>
<td>12/12 undetectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 2.1 pmol/L</td>
</tr>
<tr>
<td>Anastrozole¹</td>
<td>97.3</td>
<td>9/12 undetectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 2.6 pmol/L</td>
</tr>
<tr>
<td>Exemestane²</td>
<td>97.9</td>
<td>7/9 undetectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 2.8 pmol/L</td>
</tr>
</tbody>
</table>

AI = Aromatase inhibitor.

Aromatase Inhibition Is Associated With Higher Rate of Estrogen Depletion Compared With PMW

PMW = Postmenopausal women; BC = Breast cancer; AI = Aromatase inhibitor.

Bone Architecture is Compromised by Estrogen Deficiency and Increased Bone Turnover


Normal

Osteoporosis
Decrease in Bone Mineral Density (BMD) is associated with fracture risk. The graph shows the correlation between BMD T-score (standard deviation, SD) and fracture risk. BMD T-scores range from normal to osteopenia to osteoporosis. The fracture risk increases as the BMD T-score decreases, with a 4X increase for osteopenia and 8X and 16X increases for osteoporosis.
80% of Fractures Occur in Women Who Are Not Osteoporotic

- Fracture rate increases ~2-fold in osteopenic women
- Majority of fractures occur in osteopenic women (T-Score between -1.0 to -2.5)

All AIs Increase Fracture Risk


AI = Aromatase inhibitor.

1. ATAC (68 months)
2. IES (58 months)
3. BIG 1-98 (26 months)
4. MA.17 (30 months)

P-values:
- ATAC: P < .0001
- IES: P = .003
- BIG: P < .001
- MA: P = .25

Fractures, %

- Letrozole: 11%
- Placebo: 7.7%
- Exemestane: 5.7%
- Tamoxifen: 4.6%
- Anastrozole: 5.3%
Fractures
(occurring at any time before recurrence)

<table>
<thead>
<tr>
<th>Fractures before recurrence</th>
<th>A N=3092 (%)</th>
<th>T N=3094 (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with one or more fracture episodes</td>
<td>421 (13.6)</td>
<td>311 (10.1)</td>
<td>1.41</td>
<td>1.21-1.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hip</td>
<td>49 (1.6)</td>
<td>42 (1.4)</td>
<td>1.17</td>
<td>0.75-1.82</td>
<td>0.46</td>
</tr>
<tr>
<td>Spine</td>
<td>60 (1.9)</td>
<td>37 (1.2)</td>
<td>1.64</td>
<td>1.08-2.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Wrist / colles</td>
<td>94 (3.0)</td>
<td>83 (2.7)</td>
<td>1.14</td>
<td>0.84-1.54</td>
<td>0.4</td>
</tr>
<tr>
<td>All other sites</td>
<td>270 (8.7)</td>
<td>191 (6.2)</td>
<td>1.46</td>
<td>1.20-1.77</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

A, anastrozole; T, tamoxifen
Fracture episode rates throughout the study

<table>
<thead>
<tr>
<th>Time since randomisation (years)</th>
<th>Annual fracture episode rates (%)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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</tbody>
</table>

At risk:
A  2984  2859  2745  2640  2496  2306  2077  1713  702
T  2976  2824  2699  2572  2419  2208  2000  1645  659
Bone Loss in Breast Cancer and Its Management
Different Classes of Bisphosphonates

- **Etidronate**
- **Pamidronate**
- **Clodronate**
- **Tiludronate**
- **Alendronate**
- **Risedronate**
- **Zoledronic acid**
- **Ibandronate**

Relative Potency of Bisphosphonates

**Relative Potency in vivo (rat)**

<table>
<thead>
<tr>
<th>ED50</th>
<th>10^-10</th>
<th>10^-9</th>
<th>10^-8</th>
<th>10^-7</th>
<th>10^-6</th>
</tr>
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<tbody>
<tr>
<td>Etidronate</td>
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<td>Clodronate</td>
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<td>Dimethyl-APD</td>
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<td>Alendronate</td>
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<td>Risedronate</td>
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**Relative Potency in vitro (IC50)**

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</table>

Graph showing the relative potency of bisphosphonates with logarithmic scales on both axes.
Zoledronic Acid and Bone Health Management- AIBL
Zoledronic Acid Increases BMD in Postmenopausal Women With Low BMD

Ongoing Trials of Zoledronic Acid For Prevention of Aromatase Inhibitor-Induced Bone Loss (AIBL)

- Premenopausal
  - ABCSG-12 (n= 401)

- Postmenopausal
  - Z-FAST (n= 602)
  - ZO-FAST (n=1,066)
  - E-ZO-FAST (n= 526)

Total of patients treated with Zoledronic acid n= 2,595
ABCSG-12: BMD in Premenopausal Women Receiving Adjuvant Hormonal Therapy

- Accrual 1999 to 2006
- 1,800 premenopausal ♀
- Bone sub-study (n= 401)
- Stage I & II, < 10 pos nodes, ER+ and/or PgR+
- Treatment duration: 3 years
- Preoperative CT allowed

Surgery (+XRT)  →  Goserelin 3.6 mg/28 days  →  

Tamoxifen + Zoledronic acid (4 mg)* q 6 mo

Randomize

Baseline BMD  →  6-month BMD

Tamoxifen

Anastrozole + Zoledronic acid (4 mg)* q 6 mo

Anastrozole

3 years, final BMD


ABCSG-12 = Austrian Breast and Colorectal Cancer Study Group Trial 12; BMD = Bone mineral density; CT = Chemotherapy; XRT=Preoperative radiotherapy.

*8 mg reduced to 4 mg.
ABCSG-12 (Follow-up 5 years): % BMD change at the LS

San Antonio, December 13th, 2007

M. Gnant (12)
Zoledronic Acid Preserves BMD Over 3 Years of Adjuvant Therapy

BMD = Bone mineral density; ZOL = Zoledronic acid.
Z-FAST,\textsuperscript{1} ZO-FAST\textsuperscript{2}, and E-ZO-FAST\textsuperscript{3}

Study Design

Eligibility
- ER\textsuperscript{+}/PgR\textsuperscript{+} BCa
- PMW with T-score $\geq -2$

Stratification
- Adjuvant CT (yes or no)
- T score ($> -1$ or between $-1$ and $-2$)

Accrual completed:
- Z-FAST: $N = 602$
- ZO-FAST: $N = 1066$
- E-ZO-FAST: $N = 526$

PMW = Postmenopausal women; CT = Chemotherapy. *Initiation of zoledronic acid determined by postbaseline BMD T-score $<-2.0$, any clinical fracture, or any asymptomatic fracture at 36 months.

Zoledronic Acid Initiation in Delayed Group

### Delayed Group Patients Who Initiated Zoledronic Acid

<table>
<thead>
<tr>
<th>Visit</th>
<th>All patients</th>
<th>Per protocol&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12-mo visit</strong></td>
<td>44 (14.7)</td>
<td>28 (9.3)</td>
</tr>
<tr>
<td><strong>24-mo visit</strong></td>
<td>54 (18.0)</td>
<td>37 (12.3)</td>
</tr>
<tr>
<td><strong>36-mo visit</strong></td>
<td>62 (20.7)</td>
<td>45 (15.0)</td>
</tr>
</tbody>
</table>

### First Zoledronic Acid Infusion in Delayed Group

<table>
<thead>
<tr>
<th>Time to Initiation, mo</th>
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<tbody>
<tr>
<td>Mean (SD)</td>
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<tr>
<td>13.5 (10.2)</td>
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<tr>
<td>Median</td>
</tr>
<tr>
<td>11.5</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>0.03–37.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Initiation of zoledronic acid determined by postbaseline T score < -2.0, any clinical fracture, or any asymptomatic fracture at 36 mo.

Intragroup comparisons from baseline to month 12 or 24 for all treatment groups were significant (P < .0001 for all).

Adapted from Brufsky A, et al. Presented at: 29th Annual SABCS; December 14-17, 2006; San Antonio, TX. Abstract 5060.

Z-FAST: Upfront Zoledronic Acid Increases BMD in Lumbar Spine and Hip

SEM = Standard error of the mean; BMD = Bone mineral density; ZOL = Zoledronic acid.

*P values correspond to intergroup comparisons.
†Intragroup comparisons from baseline to month 12 or 24 for all treatment groups were significant (P < .0001 for all).
‡Adapted from Brufsky A, et al. Presented at: 29th Annual SABCS; December 14-17, 2006; San Antonio, TX. Abstract 5060.

Z-FAST: Upfront Zoledronic Acid Shifts Lumbar Spine T-Score Distribution at 36 Months

BMD = Bone mineral density. *Missing includes patients discontinued from the study.
†P values correspond to intergroup comparisons at month 24.

Novartis data on file.

BMD = Bone mineral density. *Missing includes patients discontinued from the study.
†P values correspond to intergroup comparisons at month 24.

Novartis data on file.
# Fracture Rates: Z-FAST (36 months)

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>No. of Patient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upfront Group (n=300)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
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<tr>
<td>Significant trauma</td>
<td>11 (3.7)</td>
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<tr>
<td>Minimal or no trauma</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Radiological spine</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>17 (5.7)</strong></td>
</tr>
</tbody>
</table>

Additional Adverse Events: Z-FAST

- Renal disorders
  - Grade 1-2 renal failure
    - Upfront group, 2 patients
    - Delayed group, 0 patients
    - Both suspected to be related to zoledronic acid

- Atrial fibrillation
  - Grade 1-2
    - Upfront group: 3 patients
    - Delayed group: 0 patients
  - Grade 3-4
    - Upfront group: 4 patients
    - Delayed group: 4 patients
    - None suspected to be related to study drugs

- Osteonecrosis of the jaw
  - No confirmed cases
Oral Bisphosphonates Improve AIBL

- **SABRE (Van Posnak, SABCS #502, 2007):** risedronate (35 mg PO weekly) substantially improved BMD in the LS and TH at 12 months versus placebo in women receiving anastrozole as adjuvant therapy (n=144)

- **IBIS-II Sub-study (Singh, SABCS #28, 2007):** risedronate (35 mg PO weekly) substantially improved BMD in the LS and TH at 12 months versus placebo in women receiving anastrozole as prevention (n=59)

- **ARIBON (Lester, ASCO #553, 2007):** ibandronate (150 mg PO qmonth) substantially improved BMD in the LS and TH at 12 months versus placebo in women receiving anastrozole as adjuvant therapy (n=131)
The Impact of Risk Factors on the Incidence of Fracture
Who Should Be Treated With Bisphosphonates to Reduce Risk? (current guidance)

- **WHO osteoporosis guidelines**¹
  - T-Score ≤ −2.5
  - Osteopenic patients with additional strong risk factors

- **NOF guidelines**²
  - T-score < −2.0 with no risk factors
  - T-score < −1.5 with 1 or more risk factors
  - Prior vertebral or hip fracture

- **ASCO guidelines**³
  - Treat all patients with T-score ≤ −2.5
  - Breast cancer patients with T-score −1.0 to −2.0 should receive individualized therapy

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Treatment Guidelines: Women With Breast Cancer Initiating AI Therapy

Patient with breast cancer initiating AI therapy

- T-Score ≥ −2.0
  - No risk factors
    - Calcium and vitamin D supplements
    - Monitor risk status and BMD yearly

- T-Score < −2.0
  - Any 2 of the following risk factors
    - T-score < −1.5
    - Age > 65 years
    - Low BMI (< 20 kg/m²)
    - Family history of hip fracture
    - Personal history of fragility fracture after age 50
    - Oral corticosteroid use of > 6 months
    - Smoking
  - Zoledronic acid (4 mg q 6 mo) + calcium and vitamin D supplements
  - Monitor BMD yearly

AI = Aromatase inhibitor; BMD = Bone mineral density; ZOL = Zoledronic acid; BMI = Body mass index.

Implications for clinical practice

- Issues of bone loss and fracture are real
- DEXA on every pt receiving AIs? (yes)
- DEXA every other year? (yes)
- If osteopenic (T<-2.0), change to tam or add oral bisphosphonate (aledronate, risidronate)? (maybe)
- Consider zometa q6months? (soon)
SEED AND SOIL Hypothesis

“While many researchers have been studying ‘the seed,’ the properties of ‘the soil’ may reveal valuable insights into the ‘metastatic peculiarities’ in cancer cases.”

The Distribution of Secondary Growths in Cancer of the Breast

*The Lancet*, 1889
Steps Involved in Tumor Cell Metastasis From Primary Site to Bone

Primary malignant neoplasm → New vessel formation → Invasion → Embolism

- Tumor-cell proliferation
- Response to microenvironment
- Extravasation
- Adherence

Bone metastases

Multi-cell aggregates (lymphocytes, platelets)

Arrest in distant capillary bed in bone

Endothelial cell

Bisphosphonate Inhibition of Osteoclast Activity: Mechanism of Action

Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis\(^1\)

Bisphosphonates may modulate signaling from osteoblasts to osteoclasts
- Increased OPG production\(^2\)
- Decreased RANKL expression\(^3\)

Bisphosphonates are released locally during bone resorption\(^1\)

Bisphosphonates are concentrated under osteoclasts\(^1\)

New bone

Bone

Zoledronic Acid Reduces Bone, Liver and Lung Metastases in the Murine 4T1/luc Orthotopic Breast Cancer Model


*P<0.05, n=10
Z- FAST: Zometa-Femara Adjuvant Synergy Trials

- Key end points
  - **BMD;** bone markers; fractures; and time to recurrence/relapse

2,193 patients
BC stage I - IIIa

- Postmenopausal or amenorrheic due to cancer treatment
- ER$^+$ and/or PR$^+$
- T-score ≥ −2 SD

Letrozole +
zoledronic acid 4 mg q 6 months

Letrozole

Delayed zoledronic acid

If 1 of the following occurs:
- BMD T score < −2 SD
- Clinical fracture
- Asymptomatic fracture at 36 mo

Treatment duration 5 years

BMD = Bone mineral density; BC = Breast cancer; ER = Estrogen receptor; PR = Progesterone receptor; SD = Standard deviation; CT = Chemotherapy.
Z-FAST: Upfront Zoledronic Acid (4 mg q 6 months) - Disease Recurrence

<table>
<thead>
<tr>
<th>Month</th>
<th>Upfront group</th>
<th>Delayed group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12(^1)</td>
<td>1 (0.3)</td>
<td>6 (2.0)</td>
<td>Δ 1.7</td>
</tr>
<tr>
<td>24(^2)</td>
<td>7 (2.3)</td>
<td>12 (4.0)</td>
<td>Δ 1.7</td>
</tr>
<tr>
<td>36(^3)</td>
<td>9 (3.0)</td>
<td>14 (5.3)</td>
<td>Δ 2.3</td>
</tr>
</tbody>
</table>

Breast Cancer: ABCSG-12

Key End points:

**Primary:** Disease-free survival (DFS) at 5 y (TAM vs ANA, ZOL vs no-ZOL)

**Secondary:** Relapse-free survival (RFS) at 5y, OS at 3y (TAM vs ANA, ZOL vs no-ZOL)

1,800 patients

**BC stage II/III**

**Stratification:**
- BC Stage I/II
- ER+ and/or PR+
- Completely resected tumor
- Premenopausal
- < 10 axillary lymph nodes affected

*TAM = tamoxifen, ANA = anastrozole.*
Primary Endpoint: DFS
Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone
## Multivariate Adjusted HRs for Breast Cancer Incidence by Bisphosphonate Use

<table>
<thead>
<tr>
<th></th>
<th>Bisphosphonate Use</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Multivariate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rate/1000 person yr</td>
<td>Rate/1000 person yr</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>4.38</td>
<td>3.29</td>
<td>0.68</td>
<td>(0.52-0.89)</td>
</tr>
<tr>
<td>ER positive</td>
<td>3.28</td>
<td>2.56</td>
<td>0.70</td>
<td>(0.52-0.95)</td>
</tr>
<tr>
<td>ER negative</td>
<td>0.61</td>
<td>0.41</td>
<td>0.66</td>
<td>(0.31-1.39)</td>
</tr>
</tbody>
</table>

Adjusted for age, ethnicity, smoking, alcohol use, physical activity, BMI, mammogram in the last 2 years, prior hormone use, total calcium, total vitamin D, 5-yr hip fracture risk, and Gail 5-yr breast cancer risk, and stratified on WHI trial randomization arm.

Chlebowski. SABCS. 2009 (abstr 21).
AZURE: Does Adjuvant Zoledronic Acid Reduce Recurrence in Breast Cancer?

Primary end point: Disease free survival

Secondary endpoints: Bone metastases free survival, SREs, overall survival, adverse events, predictive biomarkers

First interim analysis expected 2008

3,360 patients
BC stage II/III

Stratification:
- N+/N-
- T Stage
- ER Status
- Chemotherapy type
- Pre-/ Postmenopausal
- Statins

Follow-up without treatment: 5 years for recurrence and survival

Standard Therapy
Zoledronic acid 4 mg
- 6 doses (q 3-4 wk)
- 8 doses (q 3 months)
- 5 doses (q 6 months)

Treatment duration 5 years

SREs = Skeletal-related events; BC = Breast cancer; ER = Estrogen receptor.

PI: Rob Coleman
Accrual completed February 2006
AZURE: Disease (DFS) and Invasive Disease Free Survival (IDFS)

**DFS**

Adjusted HR = 0.98
95% CI [0.85, 1.13] p=0.79

**IDFS**

Adjusted HR = 0.98
95% CI [0.85, 1.12] p=0.73

No. at risk:
- ZOL: 1681 1591 1465 1354 1243 580 83
- CONT: 1678 1583 1445 1344 1252 561 71

No. at risk:
- ZOL: 1681 1578 1443 1337 1224 570 82
- CONT: 1678 1574 1426 1316 1221 544 68

Time (years): 0 1 2 3 4 5 6 7
AZURE: Overall Survival

% Surviving

Adjusted HR = 0.85
95% CI [0.72,1.01] p=0.07
243 vs 276 deaths

No. at risk:

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>ZOL:</th>
<th>CTRL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1681</td>
<td>1678</td>
</tr>
<tr>
<td>1</td>
<td>1633</td>
<td>1632</td>
</tr>
<tr>
<td>2</td>
<td>1560</td>
<td>1551</td>
</tr>
<tr>
<td>3</td>
<td>1468</td>
<td>1473</td>
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<tr>
<td>4</td>
<td>1380</td>
<td>1364</td>
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<tr>
<td>5</td>
<td>656</td>
<td>623</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>

Zoledronic acid N= 1681
Control N= 1678
AZURE: Overall Survival by Menopausal Status

Pre, peri and unknown menopausal status

% Surviving

Adjusted HR = 1.01
95% CI [0.81,1.26] p=0.93
157 vs 156 deaths

Zoledronic acid N= 1131
Control N= 1127

No. at risk:
ZOL: 1131 1101 1051 993 932 454 70
CONT: 1127 1096 1049 1007 940 432 58

TIME (YEARS)

>5 years post-menopausal or age > 60

% Surviving

Adjusted HR = 0.71
95% CI [0.54,0.94] p=0.017
86 vs 120 deaths

Zoledronic acid N= 550
Control N= 551

No. at risk:
ZOL: 550 532 509 475 448 202 30
CONT: 551 536 502 466 424 191 28

TIME (YEARS)

Effects independent of ER
Questions Outstanding

- What about long term survival in zoledronic acid treated patients (ABSCG-12)?
- What about long term DFS with zoledronic acid and letrozole (ZO-FAST)?
- What about other bisphosphonates (B-34)?
ABCStudy-12 Trial Design

- Recruitment 1999-2006
- 1,803 premenopausal patients
- Stage I&II, ER+ and/or PgR+
- Duration of treatment: 3 years
- Only preoperative Chemo allowed
- Primary endpoint: DFS

**Surgery (+RT)** ➔ **Goserelin 3.6 mg q28d** ➔ **Randomize 1:1:1:1** ➔

- **Tamoxifen 20 mg/d**
- **Tamoxifen 20 mg/d** + **Zoledronic Acid 4 mg q6m**
- **Anastrozole 1 mg/d**
- **Anastrozole 1 mg/d** + **Zoledronic Acid 4 mg q6m**

---

Gnant M et al. NEJM 2009; 360: 679-91
Gnant M et al. ASCO 2010 Proceedings; abs #533
Gnant M et al. ASCO 2011 Proceedings; abs #520
Primary Endpoint: Disease-Free Survival

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ZOL</td>
<td>903</td>
<td>858</td>
<td>833</td>
<td>807</td>
<td>758</td>
<td>653</td>
<td>521</td>
<td>405</td>
<td>191</td>
</tr>
<tr>
<td>ZOL</td>
<td>900</td>
<td>862</td>
<td>841</td>
<td>822</td>
<td>788</td>
<td>674</td>
<td>544</td>
<td>419</td>
<td>208</td>
</tr>
</tbody>
</table>

**No ZOL** vs **ZOL**

- **Univariate**
  - Hazard ratio (95% CI): 0.72 (0.56-0.94)
  - *P* value: 0.014

- **Multiple Cox Regression**
  - Hazard ratio (95% CI): 0.71 (0.55-0.92)
  - *P* value: 0.011

ABCQG 2011
ZOL vs. No ZOL in N- and N+ Cohorts

Disease-Free Survival

**Node negative**

- No ZOL: 64/609 events
- ZOL: 48/602 events
- Hazard ratio: 0.74 (0.51-1.08)
- P value: 0.129

**Node positive**

- No ZOL: 68/275 events
- ZOL: 50/275 events
- Hazard ratio: 0.68 (0.47-0.98)
- P value: 0.037
Overall Survival: All Patients

Adjuvant endocrine therapy based on ovarian function suppression yields excellent results in premenopausal patients with HR-positive breast cancer.
Overall Survival: Zol vs No ZOL
Zoledronic Acid Improves OS Compared With Endocrine Therapy Alone

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36 (Time since randomization, months)</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ZOL 903</td>
<td>864</td>
<td>856</td>
<td>856</td>
<td>839</td>
<td>811</td>
<td>706</td>
<td>576</td>
<td>456</td>
<td>215</td>
</tr>
<tr>
<td>ZOL 900</td>
<td>868</td>
<td>858</td>
<td>858</td>
<td>849</td>
<td>818</td>
<td>708</td>
<td>587</td>
<td>454</td>
<td>232</td>
</tr>
</tbody>
</table>

Univariate
- Hazard ratio (95% CI): 0.63 (0.40-0.99)  
  - P value: 0.049 (Mantel-Cox)

Multiple Cox Regression
- Hazard ratio (95% CI): 0.61 (0.39-0.96)  
  - P value: 0.033
ZOL vs. No ZOL in N- and N+ cohorts

Overall Survival

Node negative

Overall survival, %

No ZOL 22/609 vs No ZOL 15/602
Hazard ratio (95% CI) 0.63 (0.32-1.26) P value 0.301

Node positive

Overall survival, %

No ZOL 27/275 vs No ZOL 18/275
Hazard ratio (95% CI) 0.62 (0.34-1.13) P value 0.126

Time since randomization, months

Patients at risk

No ZOL 609 599 595 583 562 486 387 300
ZOL 602 595 590 583 559 475 383 287

Patients at risk

No ZOL 135 275 265 261 256 249 220 189
ZOL 139 275 273 268 266 259 233 204

M. Gnant 25
Conclusion and Perspectives

• The anticancer effects of adjuvant zoledronic acid are now well established in endocrine-responsive patients
  – Safe and well tolerated in several phase-III trials (N > 7,000)
  – ABCSG-12, ZO-FAST, and the postmenopausal AZURE sub-group demonstrate significant outcome (including OS) benefits

• Bone-targeted treatments modify the bone (marrow) microenvironment and (may) affect cancer stem cells

• Adjuvant zoledronic acid is a successful treatment approach in early breast cancer, and should be considered in patients who fit these trials’ inclusion criteria
Long-term Survival Outcomes Among Postmenopausal Women With Hormone Receptor-Positive Early Breast Cancer Receiving Adjuvant Letrozole and Zoledronic Acid: 5-year Follow-up of ZO-FAST

R.H. de Boer,1 N. Bundred,2 H. Eidtmann,3 P. Neven,4 G. von Minckwitz,5 N. Martin,6 A. Modi,6 R. Coleman7

1Royal Melbourne Hospital, Victoria, Australia; 2South Manchester University Hospital, Academic Surgery, Education and Research Center, Manchester, UK; 3Universitäts Frauenklinik Kiel, Germany; 4Breast Clinic, UZ Gasthuisberg, Leuven, Belgium; 5German Breast Group, Frankfurt, Germany; 6Novartis Pharma AG, Basel, Switzerland; 7Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK

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ZO-FAST: Trial Design

Key endpoints
Primary: Bone mineral density (BMD) at 12 months
Secondary: BMD at 36 and 60 months, disease recurrence, fractures, safety

N = 1,065
Breast cancer
Stage I to IIIa
• Postmenopausal or amenorrhoeic due to cancer treatment
• ER+ and/or PgR+
• T-score ≥ −2.0

Letrozole + immediate zoledronic acid (IM-ZOL)
(4 mg every 6 months)

Letrozole + Delayed zoledronic acid (D-ZOL)
If 1 of the following occurs:
• BMD T-score < −2
• Clinical fracture
• Asymptomatic fracture at 36 months

Treatment duration: 5 years

Abbreviations: BMD, bone mineral density; ER, oestrogen receptor; PgR, progesterone receptor; R, randomisation.

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**ZO-FAST: Disease-Free Survival**

**ITT Population**

Disease-Free Survival, %

<table>
<thead>
<tr>
<th>Time on Study, months</th>
<th>IM-ZOL 4 mg (42 events)</th>
<th>D-ZOL 4 mg (62 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>60</td>
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<tr>
<td>30</td>
<td>50</td>
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<tr>
<td>36</td>
<td>40</td>
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<tr>
<td>42</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>54</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = 0.66; log-rank P value = .0375

**Censored Analysis**

Disease-Free Survival, %

<table>
<thead>
<tr>
<th>Time on Study, months</th>
<th>IM-ZOL 4 mg (42 events)</th>
<th>D-ZOL 4 mg (53 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>42</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>54</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = 0.62; log-rank P value = .024

---

**Abbreviations:** DFS, disease-free survival; D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

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**ZO-FAST: Overall Survival (ITT Population)**

Overall Survival, %

- IM-ZOL 4 mg (26 events)
- D-ZOL 4 mg (36 events)

HR = 0.69; log-rank P value = .196

Number at risk
- IM-ZOL: 532, 522, 511, 502, 485, 406
- D-ZOL: 533, 519, 505, 491, 480, 407

Time on Study, months

**Abbreviations:** D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

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ZO-FAST, AZURE, and ABCSG-12: DFS Comparison

ZO-FAST
Truly postmenopausal
n = 888
P value: 0.0998
Hazard Ratio: 0.71

AZURE1
> 5 yr postmenopausal
n = 1,041
P value: 0.02
Hazard Ratio: 0.75

ABCSG-122
Rendered postmenopausal (overall population)
N = 1,803
P value: 0.008
Hazard Ratio: 0.68

* Defined as naturally occurring menopause prior to diagnosis.


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Conclusions

• The 60-month follow-up of ZO-FAST trial confirms and extends the BMD improvement seen with immediate zoledronic acid as reported at earlier time points.

• There is a 34% improvement in DFS at 5 years between the immediate and delayed zoledronic acid groups, with a 3.6% absolute difference (91.9% vs 88.3%, respectively).

• As per the improved DFS results seen in the ABCSG-12 and AZURE trials (> 5 years postmenopausal subset), the data support the hypothesis that the anticancer potential of zoledronic acid might be best realized in a low-estrogen environment.

Abbreviations: BMD, bone mineral density; DFS, disease-free survival;
NSABP Protocol B-34: A Clinical Trial Comparing Adjuvant Clodronate vs. Placebo In Early Stage Breast Cancer Patients Receiving Systemic Chemotherapy and/or Tamoxifen or No Therapy – Final Analysis

AHG Paterson¹,², SJ Anderson¹,³, BC Lembersky¹,⁴, L Fehrenbacher¹,⁵, CI Falkson¹,⁶, KM King¹,⁷, LM Weir¹,⁸, AM Brufsky¹,⁹, S Dakhil¹,¹⁰, T Lad¹,¹¹, L Baez-Diaz¹,¹², JR Gralow¹³, A Robidoux¹,¹⁴, EA Perez¹⁵, P Zheng¹,³, CE Geyer¹,¹⁶, SM Swain¹,¹⁷, JP Costantino¹,³, EP Mamounas¹,¹⁸, Norman Wolmark¹,¹⁹

¹National Surgical Adjuvant Breast and Bowel Project (NSABP); ²Tom Baker Cancer Centre; ³Biostatistics, University of Pittsburgh Graduate School of Public Health; ⁴University of Pittsburgh Cancer Institute School of Medicine; ⁵Kaiser Permanente, Northern California; ⁶University of Alabama at Birmingham/ECOG; ⁷Cross Cancer Institute; ⁸British Columbia Cancer Agency; ⁹University of Pittsburgh Magee Women’s Hospital; ¹⁰Cancer Center of Kansas; ¹¹Stroger Hospital Cook County MBCCOP; ¹²San Juan MBCCOP; ¹³University of Washington/SWOG; ¹⁴Centre Hospitalier de l'Université de Montréal; ¹⁵Mayo Clinic Jacksonville/NCCSTG; ¹⁶University of Texas Southwestern Medical Center; ¹⁷Washington Cancer Institute, Washington Hospital Center; ¹⁸Aultman Health Foundation; ¹⁹Allegheny General Hospital
B-34 Study Design

STRATIFICATION
- Age (< 50, ≥ 50)
- Number of Positive Nodes (0, 1-3, 4+)
- ER / PgR Status

RANDOMIZATION

GROUP 1
Clodronate*
1600 mg/day
x 3 years

GROUP 2
Placebo*
x 3 years

*At the discretion of the investigator, patients may receive adjuvant systemic chemotherapy and/or tamoxifen, or no adjuvant.
NSABP Protocol B-34
Disease-Free Survival

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Events</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1656</td>
<td>312</td>
<td>0.91</td>
<td>0.27</td>
</tr>
<tr>
<td>Clodronate</td>
<td>1655</td>
<td>286</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data as of March 31, 2011
NSABP B-34 Hazard Ratios of RFI between Groups According to Stratification Variables

ER positive patients
ER negative patients
4+ positive nodes
1-3 positive nodes
Negative nodes
Patients 50+ at entry
Patients <50 at entry

All patients with follow-up

Clodronate better

Placebo better

Hazard Ratio
B-34 Post-hoc Analysis
Hazard Ratios of Skeletal Metastases between Groups by Age Categories (<50, 50-59, 60+)

- Patients 60+ at entry
- Patients 50-59 at entry
- Patients <50 at entry

Clodronate better Placebo better

HR=0.7

All patients with follow-up

Hazard Ratio

0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8
B-34 Post-hoc Analysis
Hazard Ratios of Non-Skeletal Metastases between Groups
by Age Categories (<50, 50-59, 60+)

Patients 60+ at entry
Patients 50-59 at entry
Patients <50 at entry

All patients with follow-up

Hazard Ratios of Non-Skeletal Metastases between Groups by Age Categories (<50, 50-59, 60+):

- **Clodronate better**
- **Placebo better**

Hazard Ratio

HR = 0.7
NSABP Protocol B-34: Women 50+ years old at entry

Distant Metastasis Free Interval

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Events</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1656</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>1655</td>
<td>60</td>
<td>0.62</td>
<td>0.003</td>
</tr>
</tbody>
</table>

% Distant Metastasis Free

Years after Randomization

Data as of March 31, 2011
Bone Microenvironment
Tumor Cell Interactions and Bone Destruction

- Stromal cell activation
- Pre-B cell expansion
- RANKL
- RANK
- Osteoclast precursor
- Osteoclast activation
- Osteoprotegerin (denosumab is humanized form)

↑ PGE$_2$
↑ IL-1, TNF-$\alpha$
D-CARE: Potential Direct Antitumor Effect of Bone-Targeting Therapy for Patients With Breast Cancer

Eligibility Criteria

- Pts with stage II/III breast cancer
- Receiving or scheduled to receive adjuvant or neoadjuvant therapy
  \[ N=4500 \]

Primary endpoint: Disease free survival

Secondary endopints:

- Standard therapy + Denosumab 120 mg SQ q3-4w x 6; q3m x 8; q6m x 5
  Vitamin D, calcium

- Standard therapy + placebo
  Vitamin D, calcium

Implications for Clinical Practice

• Adjuvant zoledronic acid appears to provide a DFS benefit when used as adjuvant therapy in women with suppressed estrogen

• Adjuvant bisphosphonates used for prevention of bone metastases?
  – In premenopausal women not on GNRH? (No)
  – In postmenopausal women or women on GNRH? (Quite possibly yes)

• An issue for thought: why does bone suppression affect breast cancer DFS in an low estrogen state? It’s time we really think about the “soil” in cancer pathogenesis