Bone Health and Bone Metastases

Dr. PN Mainwaring
Centre For Personalised NanoMedicine
AIBN@UQ
Disclosures

Lectures, Honoraria, Advisory Boards
- Astellas, BMS, Gelgene, Ipsen, Janssen, Medivation, Merck, Novartis, Pfizer, Roche/Genentech
1. Describe bony metastatic biology and address unmet questions

2. Describe comparisons between agents including benefit in metastatic setting and toxicity comparison
   - Describe recent adjuvant therapy data
   - Caucasian vs. Asian genome

3. Describe WHO list of essential medicines/QOL in advanced disease and ask whether bone directed therapy should be on the list

Management of Bone Health
Bone metastases are common in patients with advanced solid tumours.

Pain naturally most important symptom – see later.

Incidence of bone metastases (% range)

- Renal: 20–25%
- Melanoma: 14–45%
- Bladder: 40%
- Thyroid: 60%
- Lung: 30–40%
- Breast: 65–75%
- Prostate: 65–75%

Bone metastases can have serious and debilitating consequences – SREs

- Skeletal-related events (SREs) are defined as:


- Incidence untreated patients (placebo arm Kohno JCO 2005 vs next slide)
- A composite SRE endpoint is commonly used in clinical trials to evaluate the efficacy of bone-targeted agents
  - Pathological fractures may be symptomatic or identified by imaging assessments
- Recently, **symptomatic** skeletal events (SSEs) has been used as an alternative study endpoint for skeletal complications
  - Pathological fractures only included if clinically apparent (symptomatic)
- Hypercalcaemia of malignancy is an additional potential complication of bone metastases
SREs are a common complication in patients with solid tumours and bone metastases.

Cumulative incidence of on-study SREs in patients with newly diagnosed bone metastases

2013;
Use of intravenous bisphosphonates: breast cancer ~55%; prostate cancer ~20.2% and lung cancer ~15%

Patients with bone metastases and SREs have a poor prognosis vs those without SREs

Survival curves for breast cancer patients with bone metastases (n = 2216) with and without SREs

- Median survival for bone metastases without SRE: 16 months
- Median survival for bone metastases with SRE: 7 months

Data are from a population-based cohort study of 35,912 newly identified breast cancer patients conducted in Denmark (1999–2007)

Normal bone remodelling is tightly regulated

RANK Ligand is an important mediator of bone resorption

Osteoblasts release RANK Ligand

RANK Ligand binds to RANK on osteoclast precursor cells, which then develop into osteoclasts and become active

Active osteoclasts remove bone tissue (resorption)

Osteoblasts

The resultant bone lost needs to be replaced – by osteoblasts (formation)

Adapted from Boyle WJ et al. *Nature* 2003;423:337–42.}

RANK, receptor activator of nuclear factor κ B
A vicious cycle of bone destruction may develop in the presence of tumour cells

Overexpression of RANK Ligand drives increased formation, function and survival of osteoclasts, leading to excessive bone resorption.

Osteoblasts and other bone cells increase expression of RANK Ligand.

Tumour cells produce factors that stimulate osteoblasts to secrete RANK Ligand.

Bone resorption releases growth factors from the bone matrix that may perpetuate tumour activity.

Two classes of bisphosphonates

Non nitrogen-containing

- Etidronate
  - $\text{PO}_3\text{H}_2$
  - $\text{CH}_3-\text{C}^\text{OH}$
  - $\text{PO}_3\text{H}_2$

- Clodronate
  - $\text{PO}_3\text{H}_2$
  - $\text{Cl}^\text{C}-\text{Cl}$
  - $\text{PO}_3\text{H}_2$

Nitrogen-containing

More potent inhibitors of bone resorption

- Pamidronate
  - $\text{NH}_2(\text{CH}_2)_2^\text{C}^\text{OH}$
  - $\text{PO}_3\text{H}_2$

- Zoledronate
  - $\text{PO}_3\text{H}_2$

- Ibandronate
  - $\text{CH}_3(\text{CH}_2)_4^\text{N(CH}_2)_2^\text{C}^\text{OH}$
  - $\text{PO}_3\text{H}_2$

- Risedronate
  - $\text{N}(\text{CH}_2)_2^\text{C}^\text{OH}$
  - $\text{PO}_3\text{H}_2$

Powles JCO 2002 & 2017
Bisphosphonates (CALGB 70604 [Alliance])

1. Zoledronic acid iv q 3-4 weeks reduced pain and the incidence of skeletal-related events, including clinical fracture, spinal cord compression, radiation to bone, and surgery to bone by 25% to 40%\(^{1-3}\)

2. \(n = 1822, e = 795\) open-label, non-inferiority clinical trial of patients with metastatic breast (47%), prostate cancers (38%), multiple myeloma (15%)
   - Primary outcome was the proportion of patients having at least 1 skeletal-related event within 2 years after randomization.

1. Kohno J Clin Oncol. 2005
2. Saad JNCI. 2002
3. Pavlakis CochraneDatabase Syst Rev. 2005

Himelstein JAMA 2016
Primary Objective (CALGB 70604 [Alliance])

Figure 2. Cause-Specific Cumulative Incidence of Skeletal-Related Events

- Zoledronic acid every 4 wk
- Zoledronic acid every 12 wk

Wald $P = .67$
## Secondary End Points

### Table 3. Selected Secondary End Points

<table>
<thead>
<tr>
<th>Secondary End Points</th>
<th>Zoledronic Acid Dose Group</th>
<th>Zoledronic Acid 4-wk Dose Group Minus 12-wk Dose Group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Every 4 wk</td>
<td>Every 12 wk</td>
<td></td>
</tr>
<tr>
<td><strong>Brief Pain Inventory score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst pain</td>
<td>0.021</td>
<td>0.022</td>
<td>-0.001 (-0.022 to 0.021)</td>
</tr>
<tr>
<td>Least pain</td>
<td>0.013</td>
<td>0.007</td>
<td>0.006 (-0.008 to 0.021)</td>
</tr>
<tr>
<td>Average pain</td>
<td>0.011</td>
<td>0.008</td>
<td>0.003 (-0.014 to 0.02)</td>
</tr>
<tr>
<td>Current pain</td>
<td>0.018</td>
<td>0.016</td>
<td>0.002 (-0.014 to 0.018)</td>
</tr>
<tr>
<td>Composite pain</td>
<td>0.022</td>
<td>0.021</td>
<td>0.001 (-0.017 to 0.019)</td>
</tr>
<tr>
<td>Relief from pain</td>
<td>0.016</td>
<td>0.009</td>
<td>0.007 (-0.018 to 0.032)</td>
</tr>
<tr>
<td>Interference</td>
<td>0.019</td>
<td>0.023</td>
<td>-0.004 (-0.023 to 0.015)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0.025</td>
<td>0.024</td>
<td>0.001 (-0.005 to 0.008)</td>
</tr>
<tr>
<td><strong>Osteonecrosis of the Jaw, No./total available for analysis (%)</strong></td>
<td>18/911 (2.0)</td>
<td>9/911 (1.0)</td>
<td>1.0 (-0.2 to 2.2)</td>
</tr>
<tr>
<td><strong>Kidney dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine level, No./total available for analysis (%)</td>
<td>10/852 (1.2)</td>
<td>4/837 (0.5)</td>
<td>0.7 (-0.3 to 1.7)</td>
</tr>
<tr>
<td>Increased creatinine level vs baseline level, No./total available for analysis (%)</td>
<td>174/875 (19.9)</td>
<td>137/882 (15.5)</td>
<td>4.4 (0.7 to 8.0)</td>
</tr>
<tr>
<td><strong>Skeletal morbidity rate, mean (median) [IQR]</strong></td>
<td>0.4 (0) [0-0.5]</td>
<td>0.4 (0) [0-0.5]</td>
<td></td>
</tr>
<tr>
<td>Total available for analysis</td>
<td>882</td>
<td>884</td>
<td></td>
</tr>
<tr>
<td>Total person-years of follow-up</td>
<td>1397.5</td>
<td>1367.8</td>
<td></td>
</tr>
</tbody>
</table>
Denosumab inhibits RANK Ligand

- Denosumab is an \(\text{IgG}_2\) fully human mAb binds h-RANK Ligand with high affinity & specificity\(^1-3\)
- By binding to RANK Ligand, denosumab prevents RANK Ligand from activating its receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone surface\(^1,2\)
  - Denosumab mimics the effects of OPG on RANK Ligand\(^2\)
- Safety: In the phase 3 clinical trials, no neutralising antibodies were detected\(^3-5\)


OPG = osteoprotegerin
RANK, receptor activator of nuclear factor kappa \(\beta\)
In metastatic bone disease, RANK-RANK Ligand signalling mediates a ‘vicious cycle’ of interaction between tumour cells and bone.

- Denosumab inhibits the ‘vicious cycle’ by binding to RANK Ligand to block osteoclast differentiation and activation\(^1\)\(^–\)\(^3\)

- Bisphosphonates inhibit the vicious cycle by embedding in bone and inducing apoptosis of activated osteoclasts\(^4\)

Three pivotal Phase III trials of denosumab vs zoledronic acid in patients with bone metastases from advanced cancer

- Primary endpoint: time to first on-study SRE (non-inferiority)
- Secondary endpoints: time to first on-study SRE (superiority); time to first and subsequent on-study SRE; safety and tolerability


*Excluding breast and prostate.
Denosumab was superior to zoledronic acid for SRE prevention¹

- Time to first on-study SRE reached almost 28 mo on denosumab
- Denosumab significantly reduced the total SREs vs. zoledronic acid

# Adverse events

<table>
<thead>
<tr>
<th>Patient incidence, n (%)</th>
<th>Zoledronic acid (n = 2836)</th>
<th>Denosumab (n = 2841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (AEs), all grades</td>
<td>2745 (96.8)</td>
<td>2734 (96.2)</td>
</tr>
<tr>
<td>Most common AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>895 (31.6)</td>
<td>876 (30.8)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>859 (30.3)</td>
<td>771 (27.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>766 (27.0)</td>
<td>769 (27.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>747 (26.3)</td>
<td>718 (25.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>694 (24.5)</td>
<td>656 (23.1)</td>
</tr>
<tr>
<td>CTCAE grade 3, 4 or 5</td>
<td>2009 (70.8)</td>
<td>2000 (70.4)</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>280 (9.9)</td>
<td>270 (9.5)</td>
</tr>
</tbody>
</table>

## Safety results of interest

<table>
<thead>
<tr>
<th>Patient incidence, n (%)</th>
<th>Zoledronic acid (n = 2836)</th>
<th>Denosumab (n = 2841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious AEs</td>
<td>1218 (42.9)</td>
<td>1233 (43.4)</td>
</tr>
<tr>
<td>Infectious serious AEs</td>
<td>572 (20.2)</td>
<td>246 (8.7)</td>
</tr>
<tr>
<td>Acute phase reactions (first 3 days)</td>
<td>37 (1.3)</td>
<td>52 (1.8)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>141 (5.0)</td>
<td>273 (9.6)</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>141 (5.0)</td>
<td>273 (9.6)</td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>18 (0.6)</td>
<td>28 (1.0)</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>280 (9.9)</td>
<td>270 (9.5)</td>
</tr>
</tbody>
</table>

Characteristics

- **ECOG performance status**
  - 0: 396/1120
  - ≥1: 635/1640

- **Location of bone metastases**
  - Axial only: 260/672
  - Appendicular only: 144/345
  - Axial and appendicular: 340/833

- **Number of bone metastases**
  - <2: 599/1696
  - ≥2: 436/1072

- **Presence or absence of visceral metastasis**
  - Yes: 403/1152
  - No: 632/1616

- **uNTx level†**
  - ≥43.7 nmol/mmol: 474/1222
  - <43.7 nmol/mmol: 458/1246
  - Overall: 1035/2768

- Hazard Ratio: Favors denosumab to Favors zoledronic acid
Breast Cancer

First SRE – Baseline characteristics

- ECOG performance status:
  - 0
  - ≥1

- Number of bone metastases:
  - <2
  - ≥2

- Presence or absence of visceral metastasis:
  - Yes
  - No

- uNTx level:
  - ≥43.7 nmol/mmol
  - <43.7 nmol/mmol

- Overall

Lipton A, EJC 2015
A study comparing denosumab administered every 4 weeks vs every 12 weeks in patients with metastatic breast cancer and metastatic prostate cancer is currently under way in Switzerland with an expected completion date of 2022.

Bone metastases are the most common cause of pain in advanced cancer patients.

Bone metastases lead to:
- Chemical mediators
- Increased pressure within bone
- Microfractures
- Stretching of periosteum
- Reactive muscle spasm
- Nerve root infiltration
- Nerve compression

Bone pain

Bone pain reduces patient functional independence and quality of life

Bone pain

**CHRONIC**
Continuous, dull, aching or throbbing pain
Severity increases with disease progression

**ACUTE**
‘Breakthrough’ pain or incident (SRE) pain
Occurs spontaneously or when weight is put on an affected bone

Reduced functional independence and quality of life

The majority of patients with bone metastases report having pain

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion of patients (%)(^\dagger) (N = 5544)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain status</td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>15.5</td>
</tr>
<tr>
<td>Mild pain</td>
<td>36.1</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>21.9</td>
</tr>
<tr>
<td>Severe pain</td>
<td>26.5</td>
</tr>
<tr>
<td>Analgesic use</td>
<td></td>
</tr>
<tr>
<td>No analgesic use</td>
<td>47.8</td>
</tr>
<tr>
<td>Opioid-based analgesic use</td>
<td>35.0</td>
</tr>
</tbody>
</table>

Typically bone pain is not adequately managed\(^2\)

\(^1\)Data are pooled baseline data for patients in the three pivotal Phase III denosumab SRE prevention studies. Analysis excludes patients with multiple myeloma.

Pain worsening in patients on denosumab vs zoledronic acid by tumour type

**Breast**
- **Denosumab:** 176 days, **HR = 0.78** (95% CI, 0.67–0.92)
- **Zoledronic acid:** 295 days

**Prostate**
- **Denosumab:** 148 days, **HR = 0.89** (95% CI, 0.77–1.04)
- **Zoledronic acid:** 177 days

**Other solid tumours**
- **Denosumab:** 103 days
- **Zoledronic acid:** 143 days, **HR = 0.81** (95% CI, 0.67–0.99)

+ 119 days

+ 29 days

+ 40 days

†Time to worst pain score > 4 points among patients with no or mild pain (0–4) at baseline. ‡Excluding breast and prostate. Data converted from months based on 1 month = 30.4 days.
Median time to increased pain interference was significantly longer with denosumab vs zoledronic acid for all 3 interference measures.¹

Time to clinically meaningful increase (ie ≥ 2-point increase) in pain interference among patients with no or mild pain at baseline

<table>
<thead>
<tr>
<th>Activity score</th>
<th>Affect score</th>
<th>Overall score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity</strong></td>
<td><strong>Affect</strong></td>
<td><strong>Overall</strong></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Denosumab</td>
<td>Denosumab</td>
</tr>
<tr>
<td>7.6</td>
<td>9.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Zoledronic acid</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td>6.0</td>
<td>7.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

- General activity
- Walking ability
- Normal work
- Mood
- Relations with others
- Enjoyment of life
- Activity + affect + sleep

Fewer patients on denosumab progressed from no or low analgesic use to strong opioid use vs zoledronic acid

Patients progressing from no or low analgesic use (AQA ≤ 2) to strong opioid use (AQA ≥ 3)*†

<table>
<thead>
<tr>
<th>Study month</th>
<th>Denosumab (n = 2174)</th>
<th>Zoledronic acid (n = 2144)</th>
<th>Proportion of patients (%)</th>
<th>Average relative difference, -13.4%</th>
<th>P = 0.041 overall‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analysis excludes patients with multiple myeloma.
†OME ≥ 75 mg/day;
‡Denosumab vs zoledronic acid by Generalised Estimating Equation.

Fewer patients on denosumab experienced worsening in HRQoL vs zoledronic acid

Proportion of at-risk patients with a ≥ 5-point reduction from baseline in FACT-G total score*

- Denosumab (n = 2603)
- Zoledronic acid (n = 2579)

Average relative difference, -4.1%
P = 0.005 overall†


*Analysis excludes patients with multiple myeloma
†Denosumab vs zoledronic acid by Generalised Estimating Equation
Safety

Higher risk hypocalcaemia with denosumab vs zolendronic acid (12.4% vs. 5.3%) (Body EJC 1990)
  - Not cumulative

Zolendronic acid dose reduction
  - recommended in patients mild-to-moderate renal impairment.
  - not recommended for the prevention of SREs in patients with severe renal impairment
  - cumulative dose of zoledronic acid an independent predictor of renal impairment

Rare toxicities
  - Encompass lots – so listen to patients
Osteonecrosis of Jaw

- ONJ ~1-2%, median time to onset 2.2 yrs
  - risk rises as treatment duration increases; avoid anti-angiogenesis agents
  - treatment delayed in unhealed, open, soft lesions in the mouth
  - preventative dentistry, recommended before treatment initiation

1. Maintain optimal oral hygiene
2. Administration of systemic antibiotics
3. Mouth rinses with chlorexidine
4. Chlorexidine mouth gel for local disinfection
5. Topical applied minocycline
6. Hyperbaric oxygen therapy
7. Oral irrigation with aqueous ozone
8. Treatment with teriparatide
Bone-targeted therapy ± radiotherapy is recommended in addition to analgesics in patients with bone pain

- Bone-targeted therapy is recommended, regardless of the presence of pain or prior SRE
  - These drugs delay both appearance and progression of pain, and both first and subsequent SREs

2012 ESMO clinical practice guidelines on management of cancer pain

- Bone pain?
  - Yes: Denosumab, zoledronic acid or pamidronate + antalgic radiotherapy
  - No: Denosumab, zoledronic acid or pamidronate

- Complicated bone metastases?†
  - Yes: Radiotherapy and/or surgery (when appropriate) + denosumab, zoledronic acid or pamidronate
  - No: Same strategies as uncomplicated bone metastases ± bone pain

- Prior SRE: radiotherapy, bone surgery
  - No: Denosumab, zoledronic acid or pamidronate

†Spinal cord compression or impending fracture; ‡Pamidronate only in breast cancer patients.

Bone-targeted therapy is recommended in patients with bone metastases whether they are symptomatic or not\(^1\)

2014 ESMO clinical practice guidelines on bone health in cancer

<table>
<thead>
<tr>
<th>Guidance on bone-targeted treatment (denosumab or zoledronic acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
</tr>
<tr>
<td>• Commence at diagnoses of metastatic bone disease</td>
</tr>
<tr>
<td>− In all patients with breast cancer or CRPC, whether they are symptomatic or not</td>
</tr>
<tr>
<td>− In selected patients with advanced lung cancer, renal cancer and other solid tumours if life expectancy &gt; 3 months and considered at high risk of SREs</td>
</tr>
<tr>
<td><strong>Continuation</strong></td>
</tr>
<tr>
<td>• Continue indefinitely throughout the course of the disease</td>
</tr>
<tr>
<td>− Ongoing treatment is recommended for patients with progression of underlying bone metastases, a recent SRE and/or elevated bone resorption markers(^1)</td>
</tr>
</tbody>
</table>

\(^1\)Results from clinical trials evaluating potential clinical applications of bone markers (e.g. helping to identify patients at high risk for bone metastasis or bone lesion progression) are awaited to identify the true value of bone markers in clinical practice.

CRPC, castration-resistant prostate cancer.

BONE METASTASES

A **bone modifying agent** (bisphosphonate, denosumab) should be routinely used in combination with other systemic therapy in patients with MBC and bone metastases. Three-monthly zolendronic acid seems to be not inferior to standard monthly schedule. Supplementation of calcium and vitamin D3 is mandatory, unless contraindications exist.
ASCOC/CCO Focused Guideline Update on Role of Bone-Modifying Agents in Metastatic Breast Cancer

Recommendation Updated for 2017 Guideline

- As recommended in the 2011 version of the ASCO bone-modifying agent guideline, patients with breast cancer who have evidence of bone metastases should be treated with bone-modifying agents. One bone-modifying agent is not recommended over another. If patients are treated with zoledronic acid at 4 mg IV administered over no less than 15 minutes, dosing options are every 12 weeks or every 3 to 4 weeks [Type = evidence based, benefits outweigh harms; evidence quality = high; strength of recommendation = strong].

Recommendation Updated for 2017 Guideline

- The analgesic effects of bone-modifying agents (denosumab, pamidronate, or zoledronic acid) are modest, and they should not be used alone for bone pain. The panel recommends that the current standard of care for supportive care and pain management be applied. This can include analgesia, adjunct therapies, radiotherapy, surgery, systemic anticancer therapy, and referral to supportive care and pain management. Evidence of a clinically meaningful benefit is insufficient to support the use of one bone-modifying agent over another. Further research is needed on this clinical question [Type = evidence based, benefits outweigh harms; evidence quality = low; strength of recommendation = weak].

Recommendations Unchanged From 2011 Guideline Update

- Bone-modifying agents are recommended for patients with metastatic breast cancer with evidence of bone destruction. One bone-modifying agent is not recommended over another.
- The mechanism of action, as well as the potential benefits and harms, should be taken into account when considering long-term use of bone-modifying agents.
- In patients with creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval is required; creatinine level should be monitored with each IV bisphosphonate dose.
- In patients with creatinine clearance < 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.
- All patients should have a dental examination and preventive dentistry before using a bone-modifying agent.

Van Poznak
JCO 2017
## 15 Years of Adjuvant Bisphosphonate Trial Data

### Clodronate
- Diel et al (GABG; n=302) - *NEJM* 1998
- Saarto et al (Finnish; n=299) - *JCO* 2001
- Powles et al (RMH; n=1089) - *JCO* 2002
- Paterson et al (NSABP-B34; n=3323) - *Lancet Oncol* 2012

### Zoledronic acid
- Gnant et al (ABCSG-12; n=1803) - *NEJM* 2009
- Coleman et al (AZURE; n=3360) - *NEJM* 2011
- Coleman et al (ZO-FAST; n=1065) - *Ann Oncol* 2013

- Improved outcomes on ITT analysis
- No improved outcomes on ITT analysis
Adjuvant Bisphosphonates; EBCTCG

All Recurrences

Distant Recurrences

Coleman Lancet 2015
## Bone Recurrence By Menopausal Status

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated Bisph</th>
<th>Events/Women Allocated Not</th>
<th>Bisph events Logrank Variance of O-E</th>
<th>Ratio of annual event rates Bisph : Not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal †</td>
<td>170/3134 (5.4%)</td>
<td>163/2711 (6.0%)</td>
<td>-5.3 75.0</td>
<td>0.93 (SE 0.11)</td>
</tr>
<tr>
<td>Peri-menopausal *</td>
<td>28/461 (6.1%)</td>
<td>19/367 (5.2%)</td>
<td>2.0 8.8</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>222/5737 (3.9%)</td>
<td>286/5299 (5.4%)</td>
<td>-47.8 115.7</td>
<td>0.66 (SE 0.08)</td>
</tr>
<tr>
<td>Total</td>
<td>420/9332 (4.5%)</td>
<td>468/8377 (5.6%)</td>
<td>-51.1 199.6</td>
<td>0.774 (SE 0.062) 2p = 0.0003</td>
</tr>
</tbody>
</table>

99% or 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 7.5; p = 0.02$

- Bisph better
- Not better

Treatment effect $2p = 0.0003$
Test for trend: $\chi^2 = 5.6; 2p = 0.02$

† includes women aged < 45 if unknown
* Includes women aged 45-55 if menopausal status unknown

**Significantly Reduced Bone Recurrence in Postmenopausal Women**
Mortality In Post-menopausal Women

Breast cancer mortality

- 11036 women, 1146 events
- 10-y gain 3.1% (SE 1.3)
- Logrank 2p = 0.004

All cause mortality

- 11036 women, 1524 events
- 10-y gain 2.3% (SE 1.5)
- Logrank 2p = 0.007

Option, Not:
- 18.3%
- 15.2%
- 11.2%

Bisph:
- 7.8%
- 9.9%
- 9.9%

Death rates (%/year): total rate - rate in women without recurrence & logrank analyses

Allocation
- Years 0 - 4
- Years 5 - 9
- Years 10+
- Rate ratio, from (O-E)/V
- 1.04 (SE 0.08)
- 1.80 (SE 0.14)
- 2.32 (SE 0.20)
- 0.67 (SE 0.06)
- -1.72 (SE 0.09)
- -0.8 (SE 0.05)
- 0.04 (SE 0.03)

Not
- 3.71 (SE 0.33)
- 2.45 (SE 0.15)
- 3.32 (SE 0.24)
- 0.67 (SE 0.06)
- -2.36 (SE 0.19)
- -0.8 (SE 0.05)

Bisph
- 2.07 (SE 0.11)
- 2.30 (SE 0.17)
- 2.86 (SE 0.17)
- 0.67 (SE 0.06)
- -2.36 (SE 0.19)
- -0.8 (SE 0.05)

Adjuvant Bisphosphonates; EBCTCG
Conclusions

- Adjuvant bisphosphonates reduce bone metastases and improve survival in post-menopausal women.
  - 34% reduction in risk of bone recurrence (p=0.00001).
  - 17% reduction in risk of breast cancer death (p=0.004).
  - No significant reduction in first distant recurrence outside bone
  - Risk reductions similar irrespective of ER, node status, use/non use of chemotherapy.
  - Benefits similar for aminobisphosphonates and clodronate.

- No effects apparent on disease outcomes in pre-menopausal women.

- No significant effects on non breast cancer deaths, contralateral breast cancer or loco-regional recurrence.
Trial Design ABCSG-18

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary endpoint: Time to first clinical fracture (reached March 2014)
- Secondary endpoints:
  - Fracture related secondary endpoints (Primary Analysis March 2015)
  - Disease outcome related endpoints
    - DFS – time driven analysis of disease free survival
    - OS, BMFS (will be analyzed at EoS)
- Inclusion criteria:
  - Postmenopausal women with non-metastatic adenocarcinoma of the breast
  - ER+ and/or PR+; adjuvant non-steroidal aromatase inhibitor therapy
- Exclusion criteria:
  - Prior or concurrent treatment with SERMs
  - Current or prior IV bisphosphonate administration
  - Known history of:
    - Paget’s disease
    - Cushing’s disease
    - hyperprolactinemia
    - hypercalcaemia or hypocalcaemia
    - other active metabolic bone disease

Gnant et al, Lancet 2015; 386: 433-43

This presentation is the intellectual property of Michael Gnant. Please contact michael.gnant@meduniwien.ac.at for permission to reuse.
ABCSG-18 Primary Endpoint Results (ASCO 2015)

<table>
<thead>
<tr>
<th>Number of Fractures / Patients</th>
<th>Hazard ratio vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 176 / 1,709</td>
<td>0.50 (0.39 - 0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Denosumab 92 / 1,711</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk of fracture, %

Time since randomization, months
ABCSG 18- Subgroup Tumor Size >2 cm

<table>
<thead>
<tr>
<th></th>
<th>Number of Events / Patients</th>
<th>HR (95% CI) vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>83 / 467</td>
<td>0.663 (0.47 - 0.93)</td>
<td>0.0171</td>
</tr>
<tr>
<td>Denosumab</td>
<td>58 / 479</td>
<td></td>
<td>0.0163</td>
</tr>
</tbody>
</table>
Randomly assigned (1:1), n=865 had sufficient tissue

- Standard adjuvant systemic therapy alone (control group)
- or with zoledronic acid every 3–4 weeks for six doses, then every 3–6 months until the end of 5 years.

MAF amplification FISH
Two cores in a microarray

16q23 copy number gain
Encodes MAF transcription factor
Mediates bone cancer metastases through control of PTHrP

Coleman Lancet Oncol 2017
St Gallen International Expert Consensus Conference 2017, strongly recommended the use of bisphosphonates for the adjuvant treatment of postmenopausal women with breast cancer (Coates Annals)

ESMO 2016 guidelines (Hadji ESMO 2016)

- Bisphosphonates; routine clinical practice for the prevention of CTIBL all patients with a T-score < -2.0 or > fracture risk factors
- Adj bisphosphonates for the prevention in all women ≥ 55 years
- For younger, adj bisphosphonates recommended if amennorheic > 12 mo, and /or on OFS
  - Duration of low-dose bisphosphonate treatment for premenopausal women should not exceed that of ovarian suppression (3-5 years) unless indicated in patients with low BMD
Neoadjuvant Therapy

**JONIE-1 trial**

**Eligibility**
- Primary HER2 (-) BC (Stage IIA-IIIB)
- $T \geq 3\text{cm} / T \geq 2\text{cm}$ and $N (+)$
- $PS: 0-1$(ECOG)
- $20 \text{yr} \leq \text{Age} \leq 79 \text{yr}$

**Primary endpoint**
- pCR

**Secondary endpoints**
- DFS
- pCR by baseline Ki67
- Clinical response rate
- AE
- BCS rate

**CTZ Group**
- FEC100 q3w 4 cycles $\rightarrow$
- weekly PTX 80mg/m$^2$ 12 cycles $*$
  +
  - Zoledronic acid q3-4w 7 infusions

**CT Group**
- FEC100 q3w 4 cycles $\rightarrow$
- weekly PTX 80mg/m$^2$ 12 cycles

(* PTX $\rightarrow$ FEC *)

An operation for BC is done within 5 weeks after the last pre-operative chemotherapy

Miura SABCS 2014
Neoadjuvant Therapy

San Antonio Breast Cancer Symposium
- Cancer Therapy and Research Center at UT Health Science Center – December 10-14, 2013

Disease-free survival

<table>
<thead>
<tr>
<th></th>
<th>12mo</th>
<th>24mo</th>
<th>36mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTZ</td>
<td>97.5%</td>
<td>91.4%</td>
<td>89.3%</td>
</tr>
<tr>
<td>CT</td>
<td>100%</td>
<td>88.5%</td>
<td>84.2%</td>
</tr>
</tbody>
</table>
Bone Health
The mean age at breast cancer diagnosis is 62 years

Perimenopausal or postmenopausal women,
- may already have experienced some osteopenic or osteoporotic bone loss
- Onset of menopause, declining E2 levels lead to a gradual decrease in bone mineral density (BMD) over time, with the potential for the development of postmenopausal osteoporosis
- Significant & rapid decrease in BMD may be exacerbated by the bone-destabilizing effects of aromatase inhibitors (twice normal pop’n), and some chemotherapies (60% rendered menopausal).
  - Cancer treatment-induced bone loss (CTIBL)
  - ATAC anastrozole: median BMD loss from baseline of 6.1% at the lumbar spine and 7.2% from the total hip after 5 years
Reductions in BMD increase the risk of pathologic fracture; the 3-year risk of vertebral fracture is almost fivefold greater in women with newly diagnosed breast cancer than in women in the general population.

Even in women with normal BMD, the risk of fracture in patients with breast cancer is high.

Placebo arm of ABCSG-18 incidence of pathologic fracture was 10% in individuals with normal BMD and 11% in those with low BMD.
Prophylactic Therapy

Denosumab 60 mg sc q 6 mo
   – Ellis BCRT 2009
   – ABCSG-18; relative increases in BMD at the lumbar spine, total hip and femoral neck compared with placebo (p < 0.0001)

Zoledronic Acid 4 mg q 6mo
   – Z-FAST total hip BMD (+8.9% with upfront treatment; +6.7% with delayed treatment)
   – NC03CC (Alliance); +0.58%
Individual Therapy

- Patients should be assessed for baseline fracture risk, and that BMD should be measured.
- Lifestyle changes, such as
  - increasing the amount of weight-bearing exercise
  - Stopping smoking
  - Dietary measures ensuring
    • adequate calcium intake (1000 mg/day) and vitamin D supplementation (total intake: 1000-2000 units/day)
- Early breast cancer at risk CTIBL
  - OFS; Aromatase Inhibition, chemotherapy
  - Prophylactic bisphosphonate/denosumab therapy
Prophylaxis French Cohort

- 64,438 postmenopausal women participating in the French E3N cohort;
- 2,407 first primary breast cancer cases were identified.
- The HR of breast cancer associated with exposure to BPs was 0.98 (95% CI, 0.85 to 1.12)

Table 3. HRs for Different Types of Breast Cancer Associated With Exposure to BPs (ever v never; E3N Cohort, 2004 to 2011)

<table>
<thead>
<tr>
<th>Breast Cancer Characteristic (No. women included)</th>
<th>Never Exposed to BPs</th>
<th>Ever Exposed to BPs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Cases</td>
<td>HR* (95% CI)</td>
<td>No. Cases</td>
</tr>
<tr>
<td>All breast cancers (n = 64,438)</td>
<td>2,099</td>
<td>1 (reference)</td>
<td>308</td>
</tr>
<tr>
<td>According to ER status (n = 63,950†)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>1,429</td>
<td>1 (reference)</td>
<td>199</td>
</tr>
<tr>
<td>ER−</td>
<td>255</td>
<td>1 (reference)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to invasive or in situ status (n = 64,250‡)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>1,700</td>
<td>1 (reference)</td>
<td>245</td>
</tr>
<tr>
<td>In situ</td>
<td>242</td>
<td>1 (reference)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fournier JCO 2017