Metastatic bone disease: A challenge for patients, physicians and the society

Roger von Moos MD, Chur, Switzerland
Bone metastases can result in serious and debilitating skeletal-related events (SREs)

- SREs are defined as:¹

A composite SRE endpoint is used in clinical trials to evaluate efficacy of drugs for the treatment of patients with cancer metastases to the bone

- 2-year incidence in patients with prostate cancer and bone metastases:²*
  
  - Radiation to bone: 29%
  - Pathological fracture: 22%
  - Spinal cord compression: 7%
  - Surgery to bone: 3%

- Prior SRE increases the risk of subsequent SREs³

¹ FDA guidance for industry 2007. Available at www.fda.gov (accessed January 2013);  

*Proportion of patients who experience SRE(s) in the placebo arm of a 15-month study.
SRE: Skiing related event: Most common in my region
Prostate cancer and influence on bone disease

- Initial diagnosis and therapy
- Initiate ADT
- Cancer-treatment-induced bone loss
- Hormone sensitive
- Bone metastases
- Castration resistant
- Advanced bone events
- Death

Zoledronic acid for prevention of SREs in metastatic castration-resistant prostate cancer (CRPC)

Reduced proportion of patients with ≥ 1 SRE

- Zoledronic acid 4 mg (n = 214): 33.2%
- Zoledronic acid 8/4 mg (n = 221): 38.5%
- Placebo (n = 208): 44.2%

Increased time to first SRE

Phase III study of denosumab vs zoledronic acid in CRPC patients with bone metastases

**Inclusion criteria**
- CRPC
- Bone metastases

**Exclusion criteria**
- Oral bisphosphonates for the treatment of bone metastases
- Prior IV bisphosphonates

*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.*

Study 103

Enrolled (N = 1904)

Randomisation

<table>
<thead>
<tr>
<th>Denosumab 120 mg SC Q4W + Placebo IV Q4W* (n = 950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (≥ 500 mg) and vitamin D (≥ 400 IU) daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zoledronic acid 4 mg IV Q4W* + Placebo SC Q4W (n = 951)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

Sequential testing of endpoints to demonstrate superiority

**Primary**
- Time to first on-study SRE (non-inferiority)

**Secondary**
- Time to first on-study SRE (superiority)
- Time to first and subsequent SRE(s) (superiority)

**Exploratory**
- Overall survival, disease progression, individual SREs and skeletal morbidity rate
  - Pain prevention, pain palliation, analgesic use
  - ONJ-related attributes

If the primary endpoint of non-inferiority was met, the superiority test for secondary endpoints was further tested.

SREs were defined as any of the following:
- Pathological fracture
- Radiation to bone
- Surgery to bone
- Spinal cord compression

Baseline characteristics were balanced between groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Zoledronic acid (n = 951)</th>
<th>Denosumab (n = 950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Q1, Q3) age, years</td>
<td>71 (66, 77)</td>
<td>71 (64, 77)</td>
</tr>
<tr>
<td>ECOG performance status 0 or 1, n (%)</td>
<td>886 (93)</td>
<td>882 (93)</td>
</tr>
<tr>
<td>Stratification factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with PSA ≥ 10 µg/L</td>
<td>806 (85)</td>
<td>805 (85)</td>
</tr>
<tr>
<td>Prior chemotherapy*</td>
<td>132 (14)</td>
<td>132 (14)</td>
</tr>
<tr>
<td>Prior SRE</td>
<td>231 (24)</td>
<td>232 (24)</td>
</tr>
<tr>
<td>Median (Q1, Q3) time from diagnosis of bone metastasis to randomisation, months</td>
<td>5.19 (1.31, 16.10)</td>
<td>3.94 (1.22, 15.67)</td>
</tr>
</tbody>
</table>

*Within 6 weeks before randomisation. ECOG, Eastern Cooperative Oncology Group.

Significantly longer time without an SRE with denosumab vs zoledronic acid

HR = 0.82 (95% CI, 0.71-0.95)
P = 0.08 (superiority)

18% Risk Reduction

Significantly fewer SREs with denosumab vs zoledronic acid

Time to first and subsequent SREs* (n = 1901)

RR = 0.82 (95% CI, 0.71-0.94)
P = 0.008 (superiority)

18% Risk Reduction

*Events occurring at least 21 days apart (multiple event analysis).

CASE 1
• 71-year-old patient
• Prostate cancer diagnosed in 2006 by a rise in PSA from 3 to 6 ng/ml on routine screening
• Biopsy results showed a Gleason score of 7 and he underwent radical prostatectomy
• In 2009, his PSA started to rise again and he underwent salvage external-beam radiation with hormonal treatment
• In 2011, his PSA reached 22 ng/ml while still on ADT
• A bone scan and CT scan revealed osteoblastic lesions in the lumbar spine region
  – Metastatic castration-resistant prostate cancer (mCRPC)
• He had no other symptoms and was otherwise in good health
The role of bone-targeted therapies

Our patient

Radical prostatectomy

Radiotherapy

Metastases

ADT

SRE

± symptoms

PSA (ng/ml)

Years

Courtesy of B.Tombal
Considerations on when to start bone-targeted therapy in patients with CRPC

- Patients with non-metastatic CRPC
  - Is it possible to prevent tumour metastasis to bone?

- Patients with CRPC and bone metastases
  - Before or after development of symptoms?
  - Before or after first SRE?
Question 1

- Patients with raising PSA under ADT
  1. Should be treated with bone modifying agents after the first bone metastases is seen by bone scan
  2. Should be treated with bone targeted agents only if symptoms are evident
  3. Denosumab should be preferred because denosumab is superior to zoledronic acid to decrease pain
  4. A prolongation of DFS and OS can be expected with the use of denosumab against zoledronic acid
First SRE is likely early in the remaining lifetime of a patient with bone metastases.

Prior SRE increases the risk for subsequent SRE

- Breast cancer
- Prostate cancer
- Lung cancer and other solid tumours

Patients with on-study SREs (%)

- Prior SRE
  - Breast cancer: 58
  - Prostate cancer: 51
  - Lung cancer and other solid tumours: 52

- No prior SRE
  - Breast cancer: 32
  - Prostate cancer: 47
  - Lung cancer and other solid tumours: 40

References:
SREs increase risk of death in men with CRPC and bone metastases

Survival at day 360:
- No SRE 49.7%
- ≥ 1 SRE 28.2%

P = 0.02

Delayed time to first SRE with denosumab vs zoledronic acid regardless of pain severity or SRE history

Phase III SRE prevention study in prostate cancer

Overall study population

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.82 (0.71, 0.95)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Previous SRE:

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
<th>Treatment by subgroup interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80 (0.67, 0.95)</td>
<td>0.011</td>
<td>P = 0.668</td>
</tr>
<tr>
<td>0.88 (0.67, 1.16)</td>
<td>0.368</td>
<td></td>
</tr>
</tbody>
</table>

Worst pain score at study entry:

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
<th>Treatment by subgroup interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.77 (0.63, 0.95)</td>
<td>0.014</td>
<td>P = 0.462</td>
</tr>
<tr>
<td>0.87 (0.69, 1.09)</td>
<td>0.225</td>
<td></td>
</tr>
</tbody>
</table>

Favours denosumab  
Favours zoledronic acid

## Type of first SRE

<table>
<thead>
<tr>
<th>Event</th>
<th>Zoledronic acid (n=951)</th>
<th>Denosumab (n=950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total confirmed events</td>
<td>386 (41%)</td>
<td>341 (36%)</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>203 (21%)</td>
<td>177 (19%)</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>143 (15%)</td>
<td>137 (14%)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>36 (4%)</td>
<td>26 (3%)</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>4 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

Fewer SREs with denosumab vs zoledronic acid across SRE types

- Radiation to bone: 21% (Zoledronic) vs 19% (Denosumab)
- Pathological fracture: 15% (Zoledronic) vs 14% (Denosumab)
- Spinal cord compression: 4% (Zoledronic) vs 3% (Denosumab)
- Bone surgery: <1% (both)

Overall survival was comparable between groups

HR = 1.03 (95% CI, 0.91–1.17) P = 0.65

Denosumab provides meaningful additional benefit over current standard of care

**Time to first SRE**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Time to First SRE (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10.7</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>16.3</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>17.1</td>
</tr>
<tr>
<td>Denosumab</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Question 2

• Please select the false statement
1. Substitution with Ca and Vitamin D is mandatory to avoid a secondary hyperparathyreoidism
2. Hypocalcemia after denosumab can last over several days despite substitution
3. Substitution with Ca and Vitamin D can reduce the risk of hypocalcemia remarkably
4. Acute phase reaction are more often with zoledronic acid
5. A dental check is recommended before starting a bone targeted treatment to avoid ONJ
## Side effects

**Denosumab: no adaption to renal function**

<table>
<thead>
<tr>
<th>Adverse events of interest</th>
<th>Zoledronat</th>
<th>Denosumab</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious adverse events†</td>
<td>375 (40%)</td>
<td>402 (43%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Cumulative osteonecrosis of the jaw (total)</td>
<td>12 (1%)</td>
<td>22 (2%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Year 1</td>
<td>5 (1%)</td>
<td>10 (1%)</td>
<td>.</td>
</tr>
<tr>
<td>Year 2</td>
<td>8 (1%)</td>
<td>22 (2%)</td>
<td>.</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>55 (6%)</td>
<td>121 (13%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New primary malignant disease</td>
<td>10 (1%)</td>
<td>18 (2%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Acute phase reaction (first 3 days)**

168 (18%) 79 (8%)

Denosumab provides meaningful additional benefit over current standard of care

Time to first SRE\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Median time to first SRE (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10.7*</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>16.3*</td>
</tr>
</tbody>
</table>

Time to first SRE\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Median time to first SRE (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>17.1*</td>
</tr>
<tr>
<td>Denosumab</td>
<td>20.7</td>
</tr>
</tbody>
</table>

*Based on a 30-day month.

Prolonged hypocalcemia following denosumab therapy in metastatic hormone refractory prostate cancer


26 day treatment with iv calcium, no renal insufficiency
Personal communication: 2 cases
Hypocalcemia

Integrated analysis of all pivotal trials

Ca-Vitamin D supplementation reduces the risk for hypocalcemia remarkably

Data on file, Amgen.
IS IT BETTER TO TREAT OUR PATIENTS EARLIER WITH BONE SPECIFIC AGENTS?
Treatment before the appearance of bone metastases

PSA (ng/ml) vs. Years

Metastases
± symptoms
SRE
Question 3

• The following statement is trough
  1. Several studies have shown that treatment with bone modifying agents is indicated when PSA is rising under ADT before bone metastases are evident
  2. Denosumab prolonged time to first bone metastases against placebo in mCRPC at high risk
  3. Denosumab is approved in patients with mCRPC at high risk without bone metastases
  4. ONJ does not depend with the duration of treatment with bone modifying agents
  5. Efficacy data for more than 5 years show a benefit for denosumab against zoledronic acid
Denosumab Phase III bone metastases prevention trial in CRPC

Study 147

**Key eligibility criteria**
- CRPC with:
  - PSA ≥ 8 ng/ml and/or
  - PSA DT ≤ 10 months
- No bone metastases
- No prior IV bisphosphonate use

Baseline renal function was not an eligibility criterion

N = 1435

- Primary endpoint: time to first bone metastasis or death from any cause
- Secondary endpoints: time to first bone metastasis (excluding death), overall survival

Denosumab (120 mg SC Q4W) is currently not approved for prevention of bone metastases. Denosumab is investigational in that setting.

PSA, prostate specific antigen; PSA DT, PSA doubling time.

Bone metastases-free survival

HR 0.85

Time to bone metastases

HR 0.84

Time to symptomatic bone metastases

HR 0.67

Overall survival

HR 1.01

## Overview: Side effects against placebo

<table>
<thead>
<tr>
<th>Patient Incidence, n (%)</th>
<th>Placebo (N = 705)</th>
<th>Denosumab (N = 720)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Events (AEs)</strong></td>
<td>655 (92.9)</td>
<td>676 (93.9)</td>
</tr>
<tr>
<td><strong>Most Common AEs in Either Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>156 (22.1)</td>
<td>168 (23.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>119 (16.9)</td>
<td>127 (17.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>112 (15.9)</td>
<td>123 (17.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>102 (14.5)</td>
<td>111 (15.4)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>96 (13.6)</td>
<td>108 (15.0)</td>
</tr>
<tr>
<td><strong>Serious AEs</strong></td>
<td>323 (45.8)</td>
<td>329 (45.7)</td>
</tr>
<tr>
<td><strong>Osteonecrosis of Jaw (ONJ)</strong></td>
<td>0</td>
<td>33 (4.6%)</td>
</tr>
<tr>
<td><strong>Cumulative Incidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0</td>
<td>8 (1.1)</td>
</tr>
<tr>
<td>Year 2</td>
<td>0</td>
<td>21 (2.9)</td>
</tr>
<tr>
<td>Year 3</td>
<td>0</td>
<td>30 (4.2)</td>
</tr>
<tr>
<td><strong>Hypocalcemia</strong></td>
<td>2 (0.3)</td>
<td>12 (1.7)</td>
</tr>
</tbody>
</table>

Denosumab as prevention of bone metastases

- Time to first bone metastases useful endpoint?
- No overall survival benefit
- No benefit in QOL
- Time to symptomatic bone mets was not a predefined endpoint and most patients did not have a follow up to this endpoint
- ONJ correlates with treatment duration
- No approval in this indication from FDA and EMA (EMA decision still open)
HOW LONG SHOULD WE TREAT THESE PATIENTS?
Open label follow up Studie

Adults with CRPC and bone metastases

- Denosumab 120 mg SC Q4W + Placebo IV Q4W
- Placebo SC Q4W + Zoledronic acid 4 mg IV* Q4W

Patient choice for open-label denosumab

- Denosumab 120 mg SC Q4W for 2 years

2-year survival follow-up Q12W

Daily supplementation with calcium ≥ 500 mg and vitamin D ≥ 400 IU

yes: 87% (n = 281)

## Side effects extension phase

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer¹</th>
<th>Prostate cancer²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient incidence during open-label treatment phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab → denosumab (n = 318)</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>Zoledronic acid → denosumab (n = 334)</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Denosumab → denosumab (n = 147)</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>Zoledronic acid → denosumab (n = 118)</td>
<td>89</td>
<td>53</td>
</tr>
<tr>
<td><strong>All AEs, %</strong></td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td><strong>Serious AEs, %</strong></td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td><em><em>ONJ,</em> %</em>*</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Hypocalcaemia,</strong> † ‡ %</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Grade 3 or 4, %</strong></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1. Stopeck AT, et al. SABCS 2011 [abstract P3-16-07 and poster];
ONJ incidence depending on time of treatment

<table>
<thead>
<tr>
<th>Time of Treatment</th>
<th>Series 1</th>
<th>1 Jahr Studie 103</th>
<th>2. Jahr Studie 103</th>
<th>3. Jahr Studie 146</th>
<th>Late 103 Ext Z--&gt;D</th>
<th>Late 103 Ext D--&gt;D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
<td>3%</td>
<td>4.20%</td>
<td>5.90%</td>
<td>8.20%</td>
<td></td>
</tr>
</tbody>
</table>

Fizazzi et al. Lancet Oncology 2011
Fizazi et al. ESMO 2012 Abstr. 137P
Smith Lancet 2012
ESMO supportive care guidelines on treatment of bone pain

**Treatment of pain due to bone metastases**

Zoledronic acid, denosumab or pamidronate (only in breast cancer, plus calcium and vitamin D supplementation) should be given, in addition to analgesic radiotherapy. These drugs showed to delay SREs and to reduce pain. Patients should undergo a preventive dental screening by dentistry prior to initiation the therapy with one of the drug. The optimal duration of these drugs is not completely defined.

*USE ANALGESIC THERAPY*

---

**Bone pain?**

- **Uncomplicated bone metastases**
  - zoledronic acid, denosumab, or pamidronate should be given also in absence of pain. These drugs demonstrated to delay SRE and the appearance of pain.

**Complicated bone metastases (spinal cord compression or impending fracture)?**

- **YES**
  - Radiotherapy and/or surgery should be promptly considered, when appropriate. Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the first and subsequent SREs.
  - *USE ANALGESIC THERAPY*

- **NO**
  - The same strategies suggested for uncomplicated bone metastases with or without bone pain

**Previous SRE: radiotherapy, bone surgery**

- **YES**
  - Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the first and the subsequent SREs.

- **NO**
  - Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the first and the subsequent SREs.
What new aspects do we have to integrate in our thoughts
Symptomatic skeletal events: SSE

Only symptoms from bone metastases:

• Pain

• Neurological deficits leads to:
  – X ray, CT scan MRI or Bone scan
    → Confirmation of bone metastases
    → Confirmation for myelon compression
    → Interventions like surgery or radiotherapy for fractures or risk for fractures
Multiple new treatment options for metastatic CRPC

- **Endocrine**
  - ADT
  - Abiraterone
  - MDV3100
  - Orteronel?

- **Bone-targeted treatment**
  - Zoledronic acid
  - Denosumab
  - Alpharadin

- **‘Targeted agents’**
  - Cabozantinib?
  - Tasquinimod?
  - OGX-011?
  - OGX-427?

- **Chemotherapy**
  - Docetaxel
  - Cabazitaxel

- **Immunotherapy**
  - Sipuleucel-T
  - Ipilimumab?
  - Prostvac?

- Fizazi K. ASCO 2012.

*Some of these products are not approved – please check with your local regulatory body.*
Question 3

1. Safety data have been generated for denosumab in combination with docetaxel chemotherapy in mCRPC
2. Alpharadin and denosumab have synergistic effects in delaying SREs
3. Radium 223 is more effective for the endpoint delaying time to first SRE than denosumab
4. Denosumab should be stopped during treatment with Abiraterone
New molecules and time to first SSE

Radium-223: time to first SRE

- HR = 0.64 (95% CI, 0.52-0.78)
- P < 0.0001
- Median: 12.2 months
- Placebo (n = 307)
  - Median: 6.7 months

MDV3100 (enzalutamide): time to first SRE

- HR = 0.621
- P < 0.0001
- Median: 16.7 months
- Enzalutamide (n = 800)
  - Median: 13.3 months

- + 5.5 months
- + 3.4 months

- 1. Parker C, et al. ASCO 2012;

- NYR, not yet reached.
  † Provisional data.
Conclusion

• Bone metastases are very common in patients with prostate cancer and lead to high morbidity and costs.
• Active anticancer treatment is of highest importance: many new options on the market (Radium 223, Enzalutamide)
• Antiresorptive treatment prolongs time to first and subsequent SRE in patient with mCRPC
• Denosumab is clearly superior in efficacy to zoledronic acid in mCRPC
• Treating physicians should be aware of relevant toxicities like hypocalcemia and ONJ and should do regular checks and preventive interventions
• Denosumab had no effect on renal function and no dose adjustments were required
• Denosumab for prevention in patients at risk for bone metastases: Not at the current time point
Thank you for your attention