Osteooncology and Bone Health
Osteoconology and Bone Health

- **Versionen 2002–2022:**
  Banys-Paluchowski / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedgings / Hanf / Huober / Jackisch / Janni / Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff / Reimer / Schaller / Scharl / Schütz / Seegenschmiedt / Solbach / Solomayer / Souchon

- **Version 2023:**
  Harbeck / Huober
Bisphosphonates in Metastatic Breast Cancer

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<th>Oxford LoE</th>
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Meta-analyses and Reviews (metastatic breast cancer)


Results of Phase III trials (metastatic breast cancer)

3. Body JJ, Diel IJ, Lichinitser M et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with with
metastatic bone disease; results from two randomized, placebo-controlled phase III studies. Br J Cancer 90:1133-1137, 2004


6. Rosen LS, Gordon DH, Dugan W et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 100:36-43, 2004

Clinical relevance of bone resorption marker

Bisphosphonates for bone pain control
Denosumab - Therapy of bone metastases and skeletal related complications

Progression under bisphosphonates

**Clinical relevance of bone resorption marker**

**Bisphosphonates for bone pain control**
Randomized trials – Zoledronic acid:

Randomized trials – Other bone-targeted agents
3. Lipton A, Steger GG, Figueroa J et al. Randomized Active-Controlled Phase II Study of Denosumab Efficacy and Safety in Patients With

Non-randomized studies:

Systematic reviews:
Reviews / Guidelines:

Zoledronic acid:
1. Himelstein AL, Foster JC, Khatcheressian JL et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in
Patients With Bone Metastases: A Randomized Clinical Trial. JAMA 317(1):48-58, 2017

Pamidronate:

Denosumab & bisphosphonates:

Denosumab:

Sequential therapy with different BTAs:
**Skeletal Metastases**

**Treatment with Radionuclids**

- Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain
  - $^{186}$Rhenium-hydroxyethylidene-diphosphonat
  - $^{153}$Samarium
  - $^{89}$Strontium
  - $^{223}$Radium
  - $^{177}$Lu-EDTMP
  - $^{188}$Rhenium-HEDP

**Cave:** The potential benefits should be weighed against the risk of myelosuppression and pancytopenia

### Reviews / Overview


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186$\text{Rhenium (}^{186}\text{Re-HEDP)}$

**153Samarium (153Sm-EDTMP)**

**89Strontium (89Sr-Chlorid)**

**223Ra-dichloride:**

**177Lu (Lutetium)-EDTMP**

Recommendations and Clinical Practice Guidelines:


Reviews:

Operative therapy:

Radiation therapy: Randomized studies:
**Radiation therapy: Non-randomized studies:**


**Steroids: Systematic review:**

Surgery for Bone Metastases
Technical Aspects

Spine and limbs

Oxford LoE: 3b       GR: C       AGO: +

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspace
- Tumor-Endoprothesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrae)

8. Chow E, Meyer RM, Ding K et al. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for


**Recurrent bone pain in pre-irradiated parts of the skeleton**


**Magnetic resonance-guided focused ultrasound**

Cryoablation / Radiofrequency ablation


Bisphosphonates


Side-Effects and Toxicity: Bisphosphonates (BP) and Denosumab (Dmab)

- Renal function deterioration due to IV-aminobisphosphonates 1b
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and Dmab therapy (1.4 – 2.8% / 1.3 – 3.2%) 1b
  - Association with (simultaneous) anti-angiogenetic therapies 3b
- Severe hypocalcemia (Dmab > BPs) 1b
- Acute Phase Reaction (IV Amino-BPs, Dmab) 10–30% 1b
- Gastrointestinal side effects (oral BPs) 2–10% 1b
- Atypical femur fractures (absolute risk of 11 per 10,000 person years of BP use) 2b
- Extremely rare: Uveitis / Scleritis under BP treatment 4
Denosumab

Sequential therapy
Bisphosphonates
Denosumab


9. https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf
Clodronate

Adjuvant Aminobisphosphonates

Denosumab
2. Gnant M, Frantal S, Pfeiler G et al. Long-term outcomes of adjuvant denosumab in breast cancer: Fracture reduction and survival results from 3,425 patients in the randomised, double-blind, placebo-
controlled ABCSG-18 trial. J Clin Oncol 40, 2022 (suppl 16; abstr 507)


Guidelines

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**Dosage of Adjuvant Bisphosphonates for Improvement of Survival**

- **Non-Aminobisphosphonates:**
  - Clodronate PO 1600 mg/d (Bonefos / Clodronic acid)
  - Clodronate PO 1040 mg/d (Ostac / Clodronic acid)

- **Aminobisphosphonates:**
  - Zoledronate IV 4 mg/6 m (Zometa / Zoledronic acid)
  - Ibendronate PO 50 mg/d (Bontronat / Ibandronic acid)
  - Pamidronate PO (orally not available in most countries)
  - Risedronate PO 35 mg/w*(Actonel / Risedronic acid)
  - Alendronate PO 70 mg/w (Fosamax / Alendronic acid)

  **Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years.**

Aminobisphosphonates include:
- Zoledronic acid (65%), oral ibendronate (24%), oral pamidronate (8%), oral risedronate (2%), oral alendronate (1%) (data from EBCTCG meta-analysis)


Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*  

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<td>Physical activity</td>
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<td>Avoiding immobilisation</td>
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<td>Calcium (1000–1500 mg/d)**</td>
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<td>Vitamin D3 suppl. (800–2000 U/d or 20,000 U/w)</td>
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<td>Quit smoking, reduction of alcohol</td>
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<td>B</td>
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<tr>
<td>Avoid BMI &lt; 20 kg/m²</td>
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<td>Bisphosphonates after discontinuation of Denosumab (1-2 years)</td>
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<td>Drugs approved for osteoporosis treatment in adults (see next slide)</td>
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* http://www.dv-osteologie.org/osteoporose-leitlinien
** if nutritional supply is insufficient (in combination with Vit D3 only)


**Raloxifene**

**Strontium ranelate**

**Romosozumab**