

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Version 2025.1E

## Osteooncology and Bone Health

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- **Versionen 2002–2024:**

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- **Version 2025:**

**Krug / Rody**

# Bisphosphonates in Metastatic Breast Cancer



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- **Therapy of hypercalcemia**
- **Reduction of skeletal events / complications**
- **Reduction of bone pain**
- **Increasing bone pain-free survival**
- **Treatment beyond osseous progression**
- **Use of bone resorption marker for therapy monitoring**
- **Bisphosphonates alone for pain control**

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
1a	A	++
1a	A	++
5	D	++
5	D	-
5	D	-

# Denosumab in Metastatic Breast Cancer

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- **Therapy of hypercalcemia**
- **Reduction of skeletal events / complications**
- **Reduction of bone pain**
- **Increasing bone pain-free survival**
- **Treatment beyond progression**
  - **Progression while on bisphosphonates**
- **Use of bone resorption markers for therapy monitoring**
- **Denosumab alone for pain control**

	Oxford		
	LoE	GR	AGO
	<b>1a</b>	<b>A</b>	<b>++</b>
	<b>1a</b>	<b>A</b>	<b>++</b>
	<b>1a</b>	<b>A</b>	<b>++</b>
	<b>1b</b>	<b>A</b>	<b>++</b>
	<b>5</b>	<b>D</b>	<b>++</b>
	<b>4</b>	<b>C</b>	<b>+/-</b>
	<b>5</b>	<b>D</b>	<b>-</b>
	<b>5</b>	<b>D</b>	<b>-</b>

# Skeletal Metastases

## Treatment with Radionuclids

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- **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain**

	Oxford		
	LoE	GR	AGO
■ <sup>186</sup> Rhenium-hydroxyethyliden-diphosphonat	1b	B	+
■ <sup>153</sup> Samarium	1b	B	+
■ <sup>89</sup> Strontium	1b	B	+
■ <sup>223</sup> Radium	2b	B	+
■ <sup>177</sup> Lu-EDTMP	2b	C	+
■ <sup>188</sup> Rhenium-HEDP	1b	B	+

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

# Longer-Interval vs. Standard Dosing of Bone-Targeted Agents

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- **CALGB 70604 trial**: n = 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study

SRE after 2 years:           29.5% zoledronic acid every 4 weeks  
  28.6% zoledronic acid every 12 weeks

- **OPTIMIZE-2 trial**: n = 416 women with metastatic breast cancer, prior exposure to zoledronate or pamidronate for approx. 1 year or more

SRE after 1 year:           22.0% zoledronic acid every 4 weeks  
  23.2% zoledronic acid every 12 weeks

- **REaCT-BTA trial**: n = 263 metastatic cancer (160 breast, 103 prostate)

Denosumab (n = 148), zoledronate (n = 63) or pamidronate (n = 52) q4w vs. q12w

Primary endpoint (non-inferiority of q12w vs. q4w in HRQoL) reached

Cumulative SSE after 1 year:   7.6% bone-targeted agent every 4 weeks  
  16.6% bone-targeted agent every 12 weeks (p = 0.27)

# Bone Modifying Agents for the Therapy of Bone Metastases

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
1a	A	++
2b	B	+/-
1a	A	++
1a	A	++
1a	A	+
1a	A	++
1a	A	++
1b	B	+/-
5	D	--
2b	B	+/-

- **Clodronate PO 1600 mg daily**
- **Clodronate IV 1500 mg q3w / q4w**
- **Pamidronate IV 90 mg**
  - q3w / q4w
  - q12w
- **Ibandronate IV 6 mg q3w / q4w**
- **Ibandronate PO 50 mg daily**
- **Zoledronate IV 4 mg**
  - q4w
  - q12w
- **Denosumab 120 mg SC**
  - q4w
  - q12w
- **Other dosing or schedules, e.g. from adjuvant trials or therapy of osteoporosis**
- **Planned sequential therapy with multiple agents**

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# Metastatic Bone Disease of the Spine

## Indications for surgery

**Oxford LoE: 2b**

**GR: C**

**AGO: ++**

- **Spinal cord compression**
  - With progressive neurological symptoms
  - With pathological fractures
- **Instability of the spine**
- **Lesions in pre-irradiated parts of the spine**

# Bone Metastases Acute Spinal Cord Compression / Paraplegia

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Decompression surgery, reduction of tumor volume, stabilization surgery (&lt; 24 h) and irradiation of the spine</li> </ul>	2b	C	++
<ul style="list-style-type: none"> <li>Irradiation of the spine (&lt; 24 h)                             <ul style="list-style-type: none"> <li>Radiotherapy regimen (1 x 8-10 Gy vs. multiple fractions) depending on prognosis, performance status and patient's preference</li> </ul> </li> </ul>	3b	C	++
<ul style="list-style-type: none"> <li>Immediate start of treatment</li> </ul>	1c	D	++
<ul style="list-style-type: none"> <li>Steroids (start at first symptoms)                             <ul style="list-style-type: none"> <li>- Dexamethasone 16-24 mg/d, then reduction over 2 weeks</li> </ul> </li> </ul>	2a	C	+

**Clinical trials have included patients with different tumor entities!**

# 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 titanspacer**
- **Tumor-Endoprosthesis**
- **Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor**
- **Kypho-IORT (in studies only)**
- **Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrae)**

# Metastatic Bone Disease

## Recurrent Bone Pain after RT

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

	Oxford		
	LoE	GR	AGO
■ Single dose RT *	1b	B	++
■ Fractionated RT *	1b	B	++
■ Radionuclide therapy	2b	B	+
■ Magnetic resonance-guided focused ultrasound	1b	B	+
■ Radiofrequency ablation	4	C	+
■ Cryoablation	4	C	+

\* Dose and fractionation depending on location, interval from first radiotherapy (RT), and dose and fractionation of first RT

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

LoE

- 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
- Increased fracture risk after discontinuation of Dmab 3b
- Extremely rare: Uveitis / Scleritis under BP treatment 4



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# Metastatic bone disease: Radiotherapy (RT)

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## Indications for radiotherapy for bone metastases

- **Instability (risk of fracture)**
- **Impairment of mobility**
- **Localized pain**
- **Neurologic symptoms**
- **After surgery**
  - **Omission of radiotherapy in case of R0-resection without fracture or cortical arrosion**
- **Oligometastases without above mentioned criteria**

**Reduction of radiation-induced pain flare-up by dexamethasone**

**Radiotherapy in combination with hyperthermia**

	Oxford		
	LoE	GR	AGO
Instability (risk of fracture)	1a	B	++
Impairment of mobility	1a	B	++
Localized pain	1a	B	++
Neurologic symptoms	1a	B	++
After surgery	2b	B	++
Omission of radiotherapy in case of R0-resection without fracture or cortical arrosion	4	C	+
Oligometastases without above mentioned criteria	2b	B	+/-
Reduction of radiation-induced pain flare-up by dexamethasone	1b	B	+
Radiotherapy in combination with hyperthermia	2b	B	+/-

# Radiotherapy for bone metastases: Technique and fractionation

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- Performance status, symptoms, overall prognosis/life expectancy, mechanical stability and infiltration of the epidural space/spinal cord compression should be considered.
- For patients with uncomplicated painful bone metastases, single fraction radiotherapy with 8 Gy has comparable overall pain response rates compared to fractionated radiotherapy (i.e. 5x4 or 10x3 Gy).
- However, 1x8 Gy is associated with higher rates of re-treatment and potentially increased rates of pathological fracture and metastatic spinal cord compression during the course of disease. Thus, 1x8 Gy may preferentially be used in patients with a limited life expectancy.
- Stereotactic body radiotherapy with higher doses (e.g. 2x12 Gy, 3x9-10 Gy, 5x7 Gy, 10x4.85 Gy) potentially delivers higher complete and more durable pain response rates and is associated with higher local control. Thus, it should be considered in patients with uncomplicated bone metastases and a favorable prognosis. Pre-treatment MRT is recommended to assess epidural disease and for spinal cord contouring.

# Prophylactic Radiation Therapy versus Standard of Care for Patients with High-Risk Asymptomatic Bone Metastases

A multicenter randomized controlled Phase II clinical trial

- **Cohort:** 78 adult patients (24% breast) with high-risk bone metastases (n = 122), stratified by histology and planned SOC (systemic therapy or observation), randomly assigned in a 1:1 ratio to receive RT to asymptomatic bone metastases or SOC alone.
- **Definition of High risk:** Bone met.  $\geq 2$  cm); Involvement of hip/shoulder/sacroiliac joint or long bones (1/3-2/3 of the cortical thickness), involvement of junctional spine (C7-T1/T12-L1/L5-S1) and/or posterior involvement
- **Results:** 1 year: RT vs. SOC: SRE in one of 62 bone metastases (1.6%) vs. 14 of 49 bone metastases (29%) ( $P < .001$ ) with significantly fewer patients hospitalized for SRE in the RT arm compared with the SOC arm (0 v 4,  $P = .045$ ); median follow-up of 2.5 years: OS was significantly longer in the RT arm (hazard ratio [HR], 0.49; 95% CI, 0.27 to 0.89;  $P = .018$ )

# Common Side Effects during Treatment with Bisphosphonates / Denosumab

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Drug	Acute phase- reaction	Kidney Tox.	Upper GI- tract	Diarrhea	ONJ	
Clodronate 1500 IV	0	+	0	0	0	Non-Amino.
Clodronate 1600 PO	0	0	+	+	0	Non-Amino.
Ibandronate 50 mg PO	0	0	+	0	0	Aminobisph.
Ibandronate 6 mg IV	+	0	0	0	+	Aminobisph.
Zoledronate 4 mg IV (q4w or q12w)	+	+	0	0	+	Aminobisph.
Pamidronate 90 mg IV	+	+	0	0	+	Aminobisph.
Zoledronate 4 mg IV q6m	+	0	0	0	0	Aminobisph.
Denosumab 120 mg SC q4w	+	0	0	+	+	

# Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 2a

GR: A

AGO: ++

- **During bisphosphonate or denosumab treatment, avoid any elective dental procedures involving jaw bone manipulations during treatment with bisphosphonates or denosumab**
- **Optimize dental status before start of bisphosphonate or denosumab treatment**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**
- **Recommend good oral hygiene, limiting alcohol intake and quit smoking**
- **Under adjuvant bisphosphonate therapy, ONJ is rare (< 1%)**

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# Adjuvant Bone Targeted Therapy for Improvement of Prognosis



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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Aminobisphosphonate (IV or oral)</b> <ul style="list-style-type: none"> <li>■ Postmenopausal patients or premenopausal patients under ovarian suppression*</li> </ul> </li> </ul>	1a	A	+
<ul style="list-style-type: none"> <li>■ <b>Clodronate (oral)</b> <ul style="list-style-type: none"> <li>■ Postmenopausal patients*</li> <li>■ Premenopausal patients</li> </ul> </li> </ul>	1a	A	+
<ul style="list-style-type: none"> <li>■ <b>Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)</b> <ul style="list-style-type: none"> <li>■ Stage II and III postmenopausal patients</li> </ul> </li> </ul>	1a	B	+/-
<ul style="list-style-type: none"> <li>■ <b>Denosumab (60 mg SC q6m)</b> <ul style="list-style-type: none"> <li>■ Postmenopausal patients undergoing AI therapy</li> </ul> </li> </ul>	1b	B	-
	1b	B	+/-

\* independent of the intrinsic subtype

# Dosage of Adjuvant Bisphosphonates for Improvement of Survival\*

- **Non-Aminobisphosphonates:**
  - Clodronate PO 1600 mg/d (Bonafos / Clodronic acid)
  - Clodronate PO 1040 mg/d (Ostac / Clodronic acid)
- **Aminobisphosphonates:**
  - Zoledronate IV 4 mg/6 m (Zometa / Zoledronic acid)
  - Ibandronate PO 50 mg/d (Bondronat / 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

\*Utilisation of the NHS Predict Tool to estimate the effect of bisphosphonate use on overall survival,  
<https://breast.predict.nhs.uk/tool>

# SUCCESS A trial

*(Friedl et al., JAMA Oncol 2021; 7: 1149-1157)*

**2 y ZOL (n = 1.447)**

**5 y ZOL (n = 1.540)**

**(4 mg IV every 3 mo for 2 y)**

**(4 mg IV every 3 mo for 2 y +**

**4 mg IV every 6 mo for 3 y)**

## Survival

**No differences for DFS, OS, DDFS**

Bone recurrences

n = 28

n = 25

## Adverse Events

Grade III/IV

n = 98 (5.1% of patients)

n = 159 (7.6% of patients)

SRE bone pain

3.7%

8.3%

Arthralgia

3.1%

5.1%

Fractures

n = 3

n = 14

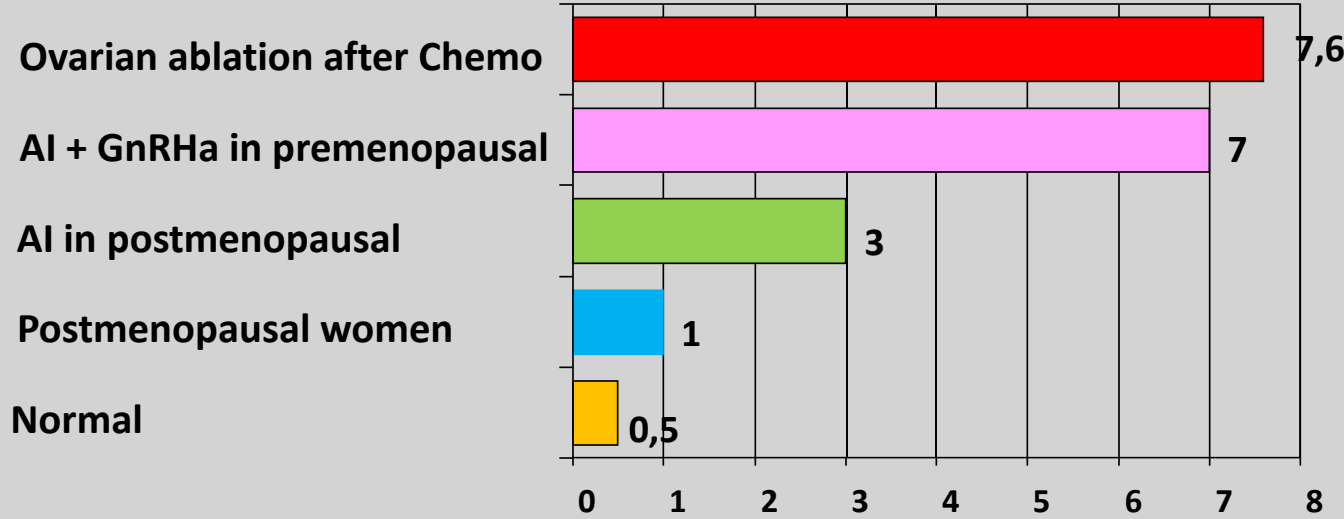
ONJ

n = 5

n = 11

# Reduction in Bone Density of Individual Agents

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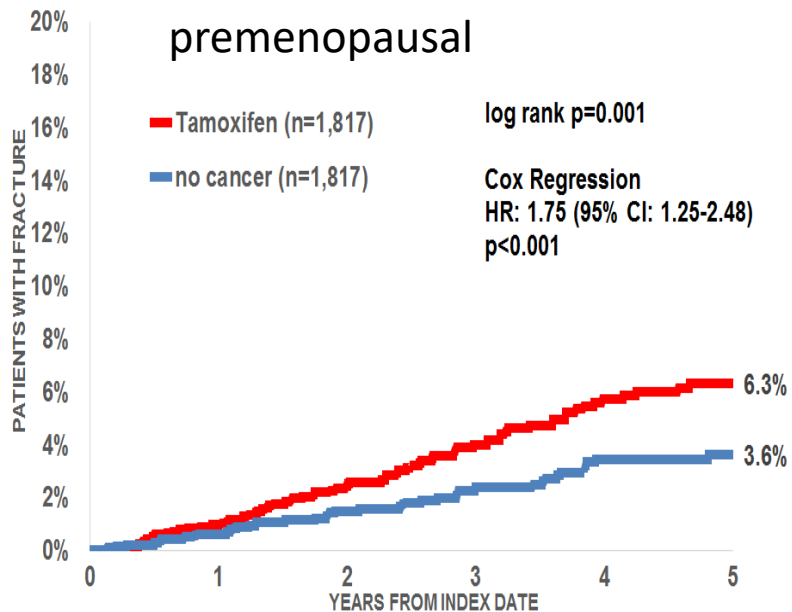
Bone mineral density (%)  
 reduction within 1 year

(1) Kanis JA Osteoporosis 22, 1997, (2) Gnant M SABCS 2004, (3) Shapiro CL, JCO 19:3305, 2001

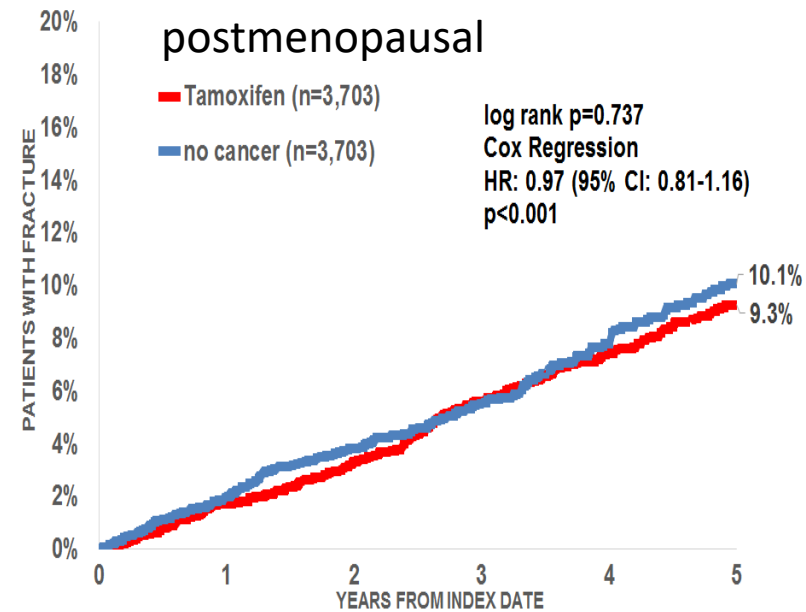
# Risk of Osteoporosis and Tamoxifen (Fracture Risk)

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	Tamoxifen	1817	1559	1215	936	720	359
No cancer	1817	1805	1335	985	738	554	



	Tamoxifen	3703	3085	2435	1887	1498	847
No cancer	3703	3629	2326	1659	1155	808	

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



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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Bisphosphonates</b> <ul style="list-style-type: none"> <li>▪ Therapy</li> <li>▪ Prevention (2–5 yrs)</li> <li>▪ after discontinuation of Denosumab (1-2 years)</li> </ul> </li> </ul>	1b	B	++
	1b	A	+
	3c	C	+
<ul style="list-style-type: none"> <li>▪ <b>Denosumab</b> <ul style="list-style-type: none"> <li>▪ Therapy</li> <li>▪ Prevention (up to max. 3 yrs)</li> </ul> </li> </ul>	1b	B	++
	1b	A	+/-
▪ <b>Hormone replacement therapy</b>	5	D	-
▪ <b>Vitamin K2 substitution</b>	2b	B	-
▪ <b>Clinical risk assessment for osteoporosis at baseline according to DVO S3 – guidelines (as of 09/2023)</b>			++
▪ <b>Routine determination of 25-hydroxyvitamin D levels</b>	3d	B	+/-
▪ <b>DXA-scan at baseline in pts with endocrine therapy and / or premature menopause</b>	5	D	+
▪ <b>Antiresorptive therapy according to DVO S3 – guidelines (as of 09/2023)</b>			++
▪ <b>Repeat DXA-scan based on risk</b>	5	D	+

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

Further recommendations (based on DVO-guidelines as of 09/2023)\*

	Oxford		
	LoE	GR	AGO
▪ <b>Physical activity</b>	4	C	++
▪ <b>Avoiding immobilisation</b>	4	C	++
▪ <b>Calcium (1000–1500 mg/d)**</b>	4	C	++
▪ <b>Vitamine D3 suppl. (800 U/d)</b>	4	C	++
▪ <b>Quit smoking, reduction of alcohol</b>	2b	B	++
▪ <b>Avoid BMI &lt; 20 kg/m<sup>2</sup></b>	3b	C	++
▪ <b>Bisphosphonates after discontinuation of Denosumab (1-2 years)</b>	3c	C	+
▪ <b>Drugs approved for osteoporosis treatment in adults (see next slide)</b>			

\* <https://dv-osteologie.org/osteoporose-leitlinien>

\*\* if nutritional supply is insufficient (in combination with Vit D3 only)

# Effect of Denosumab Discontinuation

## FREEDOM / FREEDOM Extension Trial

**n = 1001,  $\geq 2$  dose of Denosumab or placebo, follow up  $\leq 7$  months after discontinuation treatment**

Vertebral fracture rate per 100 participant year:

- 1.2 during denosumab therapy
- 7.1 after denosumab therapy
- 8.5 placebo

Non vertebral fracture rate per 100 participant year:

- 2.8 after denosumab vs. 3.8 placebo (n.s.)

**Multiple vertebral fracture (% of all vertebral fractures):**

**60.7% after denosumab therapy vs. 38.7% placebo; p = 0.049**

# Medical Treatment of Osteoporosis

	Oxford		
	LoE	GR	AGO
▪ Alendronate 70 mg PO/w*	1b	B	++
▪ Zoledronate 5 mg IV/12m*	1b	B	++
▪ Ibandronate 150 mg PO/m*	1b	B	++
▪ Ibandronate 3 mg IV/3 m	1b	B	++
▪ Risedronate 35 mg PO/w*	1b	B	++
▪ Denosumab 60 mg SC/6m*	1b	B	++
▪ Raloxifene 60 mg PO/d (improves spine only)	1b	B	+/-
▪ Parathyroid hormone 100 µg SC/d	1b	B	+
▪ Strontium ranelate 2 g PO/d**	1b	B	+
▪ Teriparatide 20 µg SC/d	1b	B	+
▪ Romosozumab 210mg s.c./m for 12m***	1b	B	+

- Alendronate 70 mg PO/w\*
- Zoledronate 5 mg IV/12m\*
- Ibandronate 150 mg PO/m\*
- Ibandronate 3 mg IV/3 m
- Risedronate 35 mg PO/w\*
- Denosumab 60 mg SC/6m\*
- Raloxifene 60 mg PO/d (improves spine only)
- Parathyroid hormone 100 µg SC/d
- Strontium ranelate 2 g PO/d\*\*
- Teriparatide 20 µg SC/d
- Romosozumab 210mg s.c./m for 12m\*\*\*

\* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis

\*\* Elevated risk of myocardial infarction (MI); only for to postmenopausal pts. with severe osteoporosis + high fracture risk

\*\*\* Elevated risk of MI and CVI; only for postmenopausal. pts with severe osteoporosis + high fracture risk

# Indication for Osteoporosis Drug Therapy

(as of 09/2023)



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## DVO Guideline Osteoporosis 2023

Short version including:

- Risk factor table for therapy threshold determination
- Tables for determining therapy thresholds (women, men)

<https://dv-osteologie.org/osteoporose-leitlinien>

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