Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Osteooncology and Bone Health

Guidelines Breast
Version 2024.1E

Osteooncology and Bone Health

- **Versionen 2002–2023:**

  Banys-Paluchowski / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich/ Friedrichs / Hanf / Harbeck / Huober / Jackisch / Janni / Kolberg-Liedtke / Lux / Maass / Nitz / Oberhoff / Reimer / Schaller / Scharl / Schütz / Seegenschmiedt / Solbach / Solomayer / Souchon

- **Version 2024:**

  Reimer / Rhiem

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Bisphosphonates in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Therapy of hypercalcemia	1a	A	++
▪ Reduction of skeletal events / complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1a	A	++
▪ Treatment beyond osseous progression	5	D	++
▪ Use of bone resorption marker for therapy monitoring	5	D	-
▪ Bisphosphonates alone for pain control	5	D	-

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Denosumab in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Therapy of hypercalcemia	1a	A	++
▪ Reduction of skeletal events / complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1b	A	++
▪ Treatment beyond progression	5	D	+
▪ Progression while on bisphosphonates	4	C	+/-
▪ Use of bone resorption markers for therapy monitoring	5	D	-
▪ Denosumab alone for pain control	5	D	-

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Skeletal Metastases
Treatment with Radionuclids

	Oxford		
	LoE	GR	AGO
▪ **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain**	1b	B	+
▪ ^{186}Rhenium-hydroxyethyliden-diphosphonat	2b	B	+
▪ ^{153}Samarium	1b	B	+
▪ ^{89}Strontium	1b	B	+
▪ ^{223}Radium	2b	B	+
▪ ^{177}Lu-EDTMP	2b	C	+
▪ ^{188} 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)

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Bone Modifying Agents for the Therapy of Bone Metastases

	Oxford		
	LoE	GR	AGO
▪ Clodronate PO 1600 mg daily	1a	A	++
▪ Clodronate IV 1500 mg q3w / q4w	1a	A	++
▪ Pamidronate IV 90 mg			
▪ q3w / q4w	1a	A	++
▪ q12w	2b	B	+/-
▪ Ibandronate IV 6 mg q3w / q4w	1a	A	++
▪ Ibandronate PO 50 mg daily	1a	A	++
▪ Zoledronate IV 4 mg			
▪ q4w	1a	A	+
▪ q12w	1a	A	++
▪ Denosumab 120 mg SC			
▪ q4w	1a	A	++
▪ q12w	1b	B	+/-
▪ Other dosing or schedules, e.g. from adjuvant trials or therapy of osteoporosis	5	D	--
▪ Planned sequential therapy with multiple agents	2b	B	+/-

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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**

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Bone Metastases Acute Spinal Cord Compression / Paraplegia

	Oxford		
	LoE	GR	AGO
▪ **Decompression surgery, reduction of tumor volume, stabilization surgery (< 24 h) and irradiation of the spine**	2b	C	++
▪ **Irradiation of the spine (< 24 h)** ▪ Radiatiotherapy regimen (1 x 8-10 Gy vs. multiple fractions) depending on prognosis, performance status and patient‘s preference	3b	C	++
▪ **Immediate start of treatment**	1c	D	++
▪ **Steroids (start at first symptoms)** **- Dexamethasone 16-24 mg/d, then reduction over 2 weeks**	2a	C	+

Clinical trials have included patients with different tumor entities!

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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-Endoprothesis
- 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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	Oxford		
	LoE	GR	AGO
Recurrent bone pain in pre-irradiated parts of the skeleton			
▪ Single dose RT *	3b	C	++
▪ Fractionated RT *	3b	C	++
▪ 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)

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	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)

	Oxford		
	LoE	GR	AGO
Bone metastases			
▪ With fracture risk	1a	B	++
▪ With functional impairment	1a	B	++
▪ With bone pain	1a	B	++
Single dose RT = fractionated RT	2a	B	++
▪ With neuropathic bone pain	1b	B	++
▪ Asymptomatic isolated bone metastasis	2b	B	+/-
▪ Reduction of radiation-induced pain flare-up by dexamethasone	1b	B	+
▪ Radiotherapy in combination with hyperthermia	2b	B	+/-

Limited studies included breast cancer patients!

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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
- **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	+	+	

Cave: Hypocalcemia under antiresorptive therapy in pts with bone metastases!

Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

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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%)**

AGSMO patientenbezogener Laufzettel
https://www.onkosupport.de/asors/content/e4125/e4405

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Adjuvant Bone Targeted Therapy for Improvement of Prognosis

	Oxford		
	LoE	GR	AGO
Clodronate (oral)			
Postmenopausal patients*	1a	A	+
Premenopausal patients	1a	B	+/-
Aminobisphosphonate (IV or oral)			
Postmenopausal patients*	1a	A	+
Premenopausal patients	1a	B	+/-
Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)			
Stage II and III postmenopausal patients	1b	B	-
Denosumab (60 mg SC q6m)			
Postmenopausal patients undergoing AI therapy	1b	B	+/-

* independent of the intrinsic subtype

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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)**
  - **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**

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SUCCESS A trial

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

	2 y ZOL (n = 1.447) **(4 mg IV every 3 mo for 2 y)**	**5 y ZOL (n = 1.540)** **(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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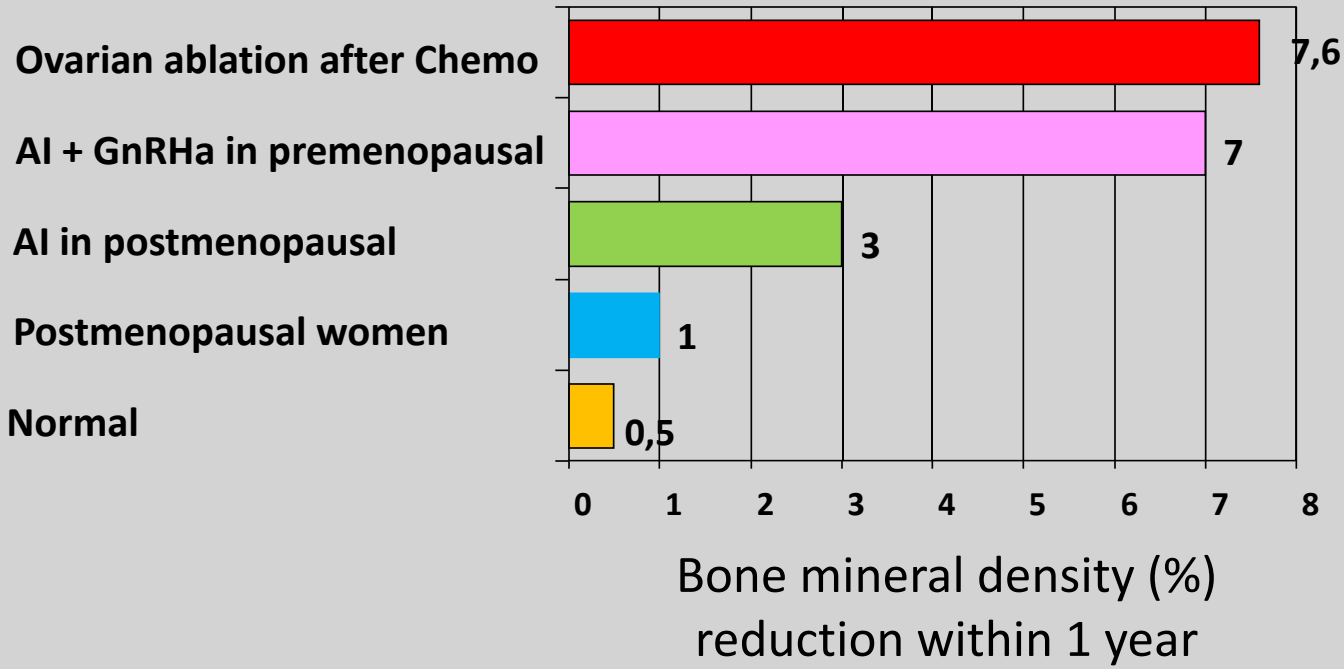

(1) Kanis JA Osteoporosis 22, 1997, (2) Gnant M SABCS 2004, (3) Shapiro CL, JCO 19:3305, 2001

Risk of Osteoporosis and Tamoxifen
(Fracture Risk)

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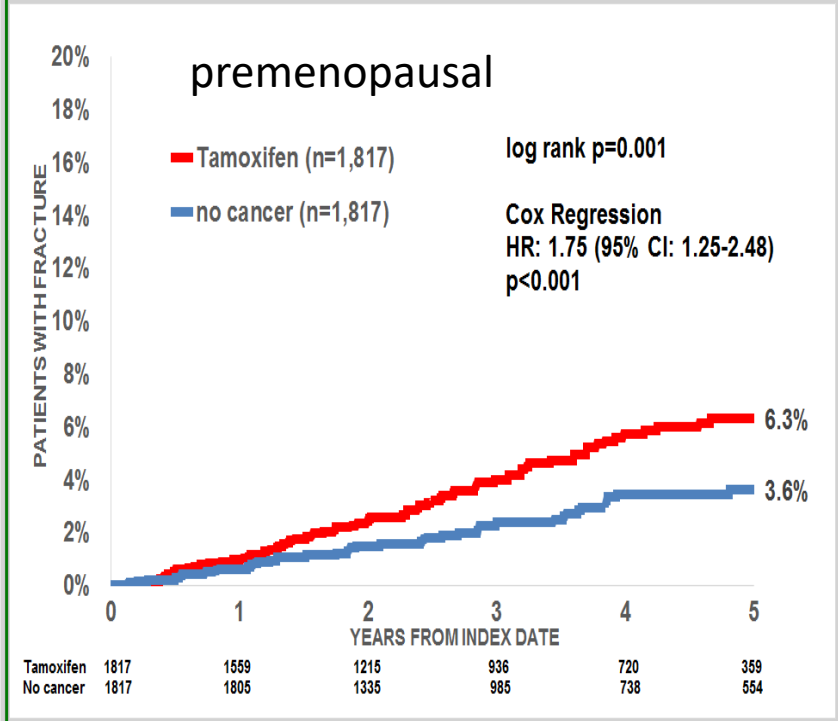

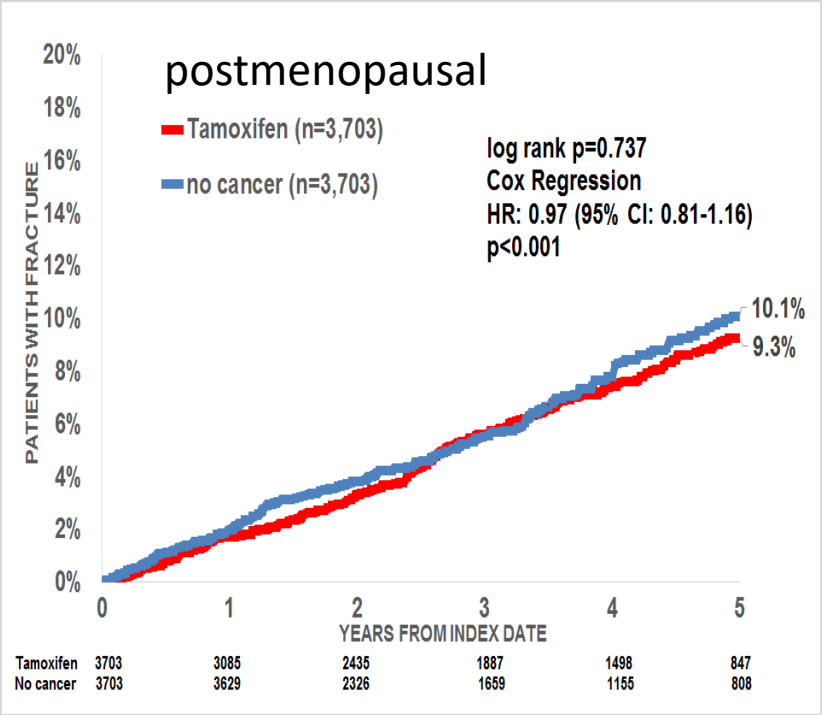

Kyvernitakis et al Osteoporosis Int 2018

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

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	Oxford		
	LoE	GR	AGO
▪ **Bisphosphonates**			
▪ Therapy	1b	B	++
▪ Prevention (2–5 yrs)	1b	A	+
▪ after discontinuation of Denosumab (1-2 years)	3c	C	+
▪ **Denosumab**			
▪ Therapy	1b	B	++
▪ Prevention (up to max. 3 yrs)	1b	A	+/-
▪ **Hormone replacement therapy**	5	D	-
▪ **Vitamin K2 substitution**	2b	B	-
▪ **Clinical risk assessment for osteoporosis at baseline according to DVO S3 – guidelines (as of 09/2023)**			++
▪ **Routine determination of 25-hydroxyvitamin D levels**	3d	B	+/-
▪ **DXA-scan at baseline in pts with endocrine therapy and / or premature menopause**	5	D	+
▪ **Antiresorptive therapy according to DVO S3 – guidelines (as of 09/2023)**			++
▪ **Repeat DXA-scan based on risk**	5	D	+

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

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

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

* 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, ≥ 2 dose of Denosumab or placebo, follow up ≤ 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**

Cummings SR et al. J Bone Miner Res 2017

Medical Treatment of Osteoporosis

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	Oxford LoE	Oxford 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	+

* 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