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# Osteooncology and Bone Health

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- **Versions 2002–2020:**

  **Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich/ Friedrichs / Hanf / Huober / Jackisch / Janni / Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solbach / Solomayer / Souchon**

- **Version 2021:**

  **Banys-Paluchowski / Kolberg-Liedtke**

# Bisphosphonates in Metastatic Breast Cancer



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| | 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 markers 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 | - |

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





- **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 | Oxford 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 | 2b | B | +/- |
| ▪ Other dosing or schedules, e.g. from adjuvant studies or osteoporosis therapy | 5 | D | -- |
| ▪ Planned sequential therapy with multiple agents | 2b | B | +/- |

# Skeletal Metastases
# Treatment with Radionuclids

| | Oxford LoE | Oxford GR | Oxford 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 | C | + |
| $^{177}$Lu-EDTMP | 2b | C | + |
| $^{188}$ Rhenium-HEDP | 1b | B | + |

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

# 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

| | 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)** | 3b | C | ++ |
| ▪ Radiatiotherapy regimen (1 x 8-10 Gy vs. multiple fractions) depending on prognosis, performance status and patient‘s preference | | | |
| ▪ **Immediate start of treatment** | 1c | D | ++ |
| ▪ **Steroids (start at first symptoms)** | 2a | C | + |

**Clinical trials 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-Endoprothesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)*
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrae)

* **Study participation recommended**

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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 | 5 | D | +/- |
| ▪ 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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# Metastatic Bone Disease
# Recurrent Bone Pain after RT

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| **Recurrent bone pain in pre-irradiated parts of skeleton** | | | |
| ▪ Single dose RT * | 3b | C | ++ |
| ▪ Fractionated RT * | 3b | C | ++ |
| ▪ Radionuclide therapy | 3b | C | + |
| ▪ Magnetic resonance-guided focused ultrasound | 1b | B | + |
| ▪ Radiofrequency ablation | 4 | C | + |
| ▪ Cryoablation | 4 | C | + |

* Dose and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.

# 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** |
| ▪ **Extremely rare: Uveitis / Scleritis under BP treatment** | **4** |

# Frequent side effects under treatment with BPs / Denosumab



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| Drug | Acute phase-reaction | Kidney Tox. | Upper GI | 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 oder 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 (LoE 2a, recommendation grade A)**
- **Optimize dental status before start of bisphosphonate or denosumab treatment (LoE 2a, recommendation grade A)**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**
- **Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended**
- **In adjuvant bisphosphonate therapy, ONJ was rare (<1%)**

**ASORS Evaluation**
**https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf**

# Adjuvant Bone Targeted Therapy for Improvement of Prognosis



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| | 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)** | | | |
| Postmenopausal patients Stage II and III | 1b | B | - |
| **Denosumab (60 mg SC q6m)** | | | |
| Postmenopausal patients undergoing AI therapy | 1b | B | +/- |

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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)**

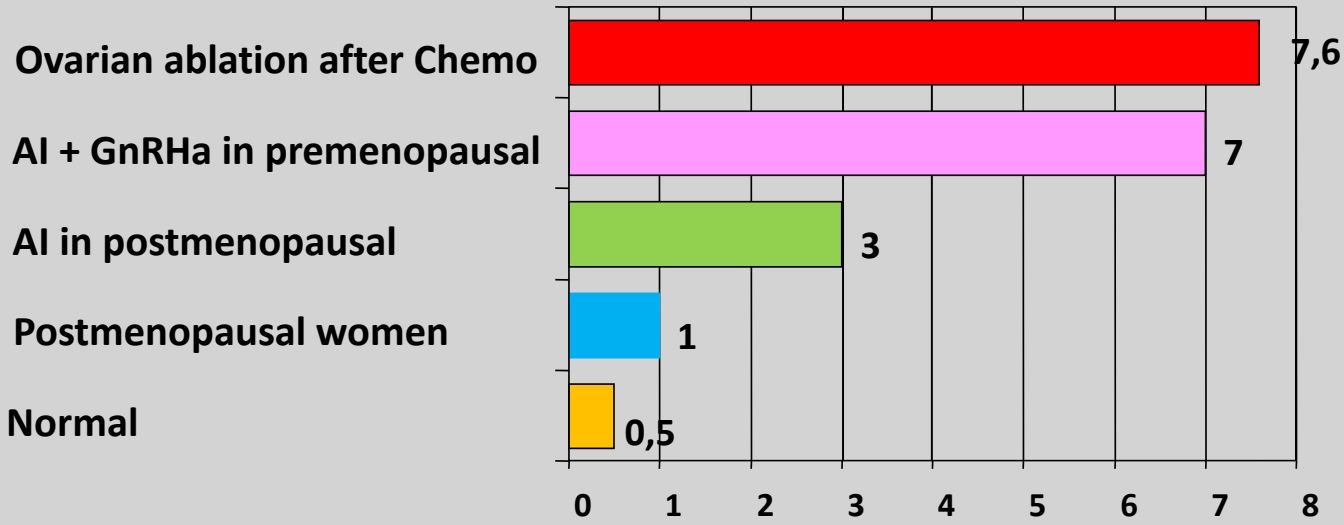
- **Aminobisphosphonates:**
  - **Zoledronate IV 4 mg/6 m (Zometa / Zoledronic acid)**
  - **Ibandronate PO 50 mg/d (Bondronat / Ibandronic acid)**
  - **Pamidronate PO (orally not available in most countries)**
  - **Risedronate PO 35 mg/w*(Actonel / Risedronic acid)**
  - **Alendronate PO 70 mg/w (Fosamax / Alendronic acid)**
  - **Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years**

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

# Reduction in bone density of individual agents








(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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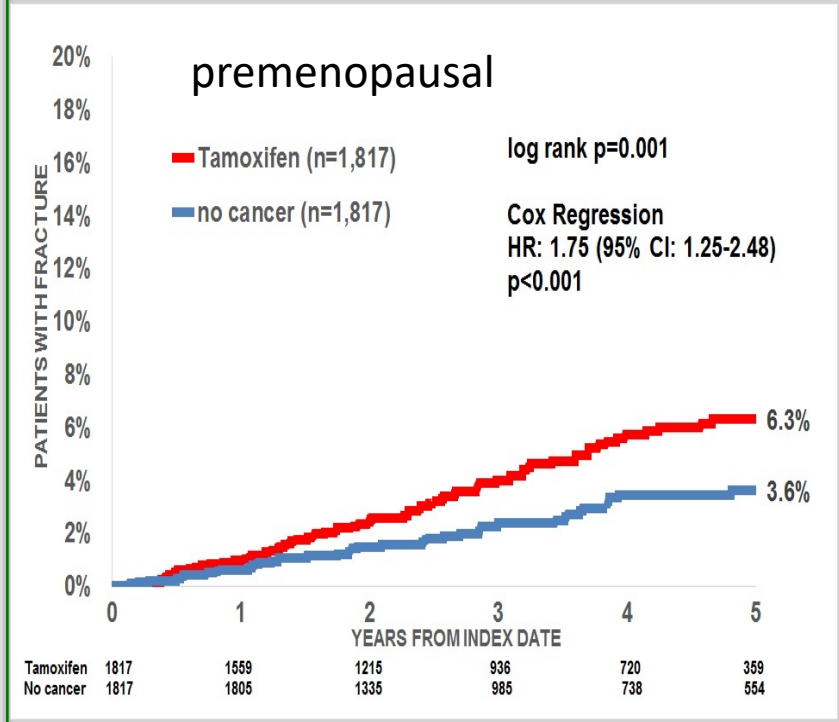


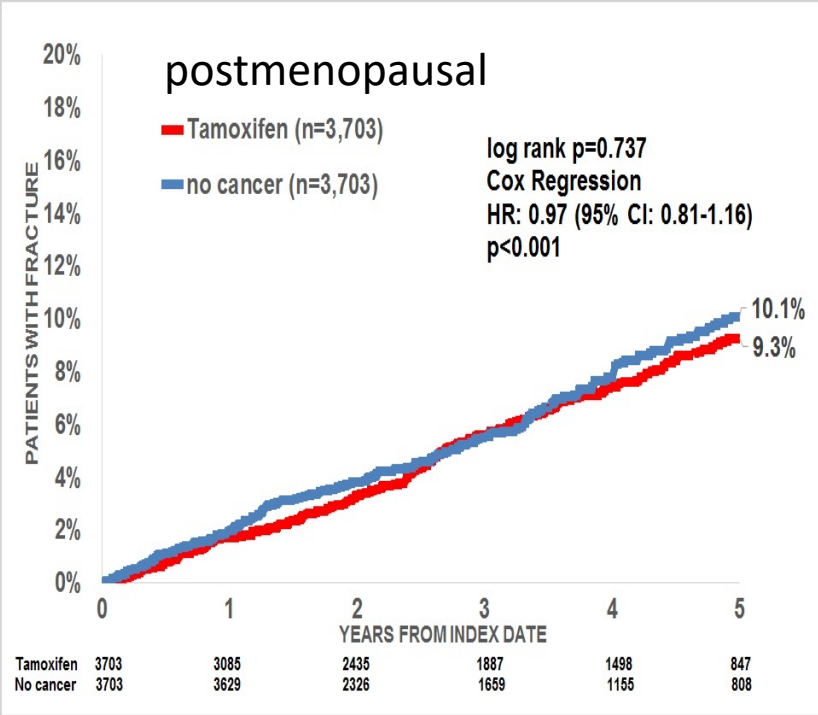


Kyvernitakis et al Osteoporosis Int 2018

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



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| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| **Bisphosphonates** | | | |
| Therapy | 1b | B | ++ |
| Prevention (2–5 yrs) | 1b | A | + |
| after discontinuation of Denosumab (time-limited) | 3c | C | + |
| **Denosumab** | | | |
| Therapy | 1b | B | ++ |
| Prevention (up to max. 3 yrs) | 1b | A | +/- |
| **Hormone replacement therapy** | 5 | D | - |
| **Clinical risk assessment for osteoporosis at baseline according to DVO S3 - guidelines** | | | ++ |
| **DXA-Scan at baseline in pts with endocrine therapy and/or premature menopause** | 5 | D | + |
| **Antiresorptive therapy according to according to DVO S3 - guidelines** | | | ++ |
| **Repeat DXA-scan based on risk** | 5 | D | + |

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



| Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)* | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| ▪ Physical activity | 4 | C | ++ |
| ▪ Avoid immobilisation | 4 | C | ++ |
| ▪ Calcium (1000–1500 mg/d)** | 4 | C | ++ |
| ▪ Vitamine D3 suppl. (800–2000 U/d or 20,000 U/w) | 4 | C | ++ |
| ▪ Stop smoking, reduction of alcohol | 2b | B | ++ |
| ▪ Avoid BMI < 20 mg/m$^2$ | 3b | C | ++ |
| ▪ Bisphosphonates after discontinuation of Denosumab (time-limited) | 3c | C | + |
| ▪ Drugs approved for osteoporosis treatment in adults (see next slide) | | | |

* http://www.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

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| ▪ Alendronate 70 mg PO/w* | 1b | B | ++ |
| ▪ Denosumab 60 mg SC/6m* | 1b | B | ++ |
| ▪ Ibandronate 150 mg PO/m* | 1b | B | ++ |
| ▪ Ibandronate 3 mg IV/3 m | 1b | B | ++ |
| ▪ Parathyroid hormone (1-84) 100 µg SC/d | 1b | B | + |
| ▪ Raloxifene 60 mg PO/d (improves spine only) | 1b | B | +/- |
| ▪ Risedronate 35 mg PO/w* | 1b | B | ++ |
| ▪ Strontium ranelate 2 g PO/d** | 1b | B | + |
| ▪ Teriparatide (1-34) 20 µg SC/d | 1b | B | + |
| ▪ Zoledronate 5 mg IV/12m* | 1b | B | ++ |

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

** Elevated risk of myocardial infarction. Substance restricted to postmenopausal pts. with severe osteoporosis and high fracture risk.

# https://www.dv-osteologie.org/uploads/Leitlinie%202017/DVO%20Leitlinie_Kitteltaschenversion_16012020.pdf

**TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSETHERAPIE NACH RISIKOPROFIL** in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.[1]

| **Lebensalter in Jahren** | | T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score > -2,0 nicht sicher belegt.) | | | | |
|---|---|---|---|---|---|---|
| **Frau** | **Mann[2]** | **-2,0 bis -2,5** | **-2,5 bis -3,0** | **-3,0 bis -3,5** | **-3,5 bis -4,0** | **< -4,0** |
| 50-60 | 60-70 | Nein | Nein | Nein | Nein | Ja |
| 60-65 | 70-75 | Nein | Nein | Nein | Ja | Ja |
| 65-70 | 75-80 | Nein | Nein | Ja | Ja | Ja |
| 70-75 | 80-85 | Nein | Ja | Ja | Ja | Ja |
| >75 | >85 | Ja | Ja | Ja | Ja | Ja |

[1] Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).
[2] bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

**Therapieindikation auch schon bei um 1,0 höherem T-Score [3,4], wenn:**
- Glukokortikoide oral ≥ 2,5 mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

**Diagram courtesy of the DVO**