Guidelines Breast
Version 2024.1E

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Osteooncology and Bone Health

Osteooncology and Bone Health

Guidelines Breast
Version 2024.1E

- **Versionen 2002–2023:**
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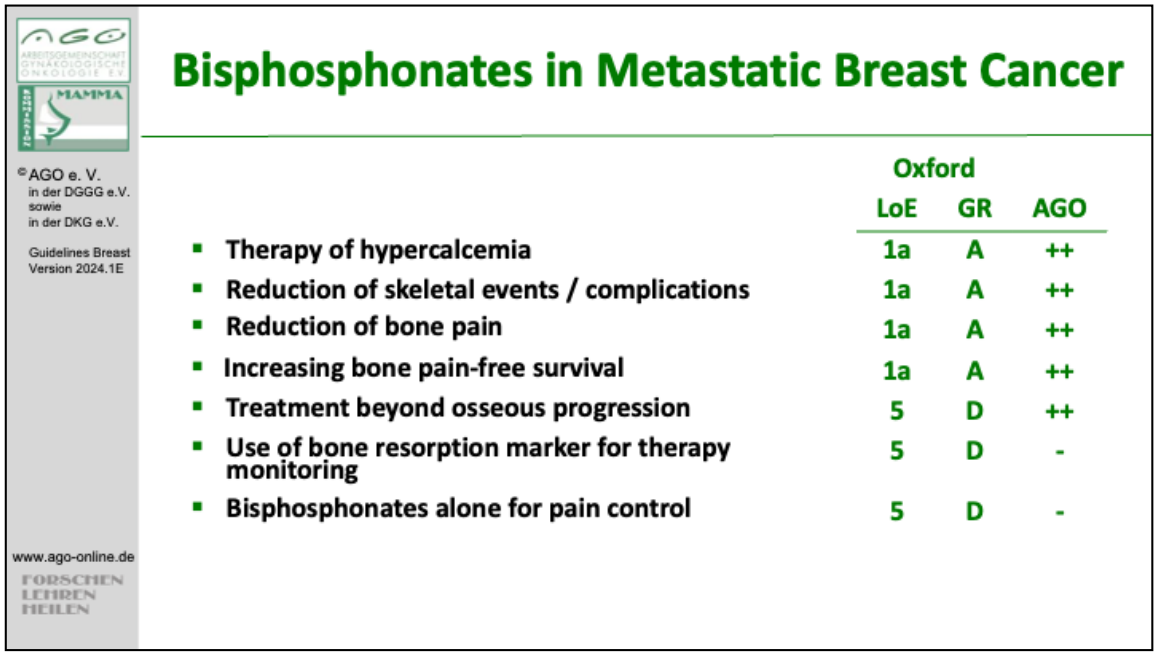


Bisphosphonates in Metastatic Breast Cancer

	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	-

Meta-analyses and Reviews (metastatic breast cancer)

1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
2. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
3. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017
4. Tesfamariam Y, Jakob T, Wöckel A et al. Adjuvant bisphosphonates or RANK-ligand inhibitors for patients with breast cancer and bone metastases: A systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2019;137:1-8.

Results of Phase III trials (metastatic breast cancer)

1. Body JJ, Diel IJ, Lichinitser MR et al. Intravenous Ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 14:1399-1405,2003
2. Diel IJ, Body JJ, Lichinitser MR et al. Improved quality of life for long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 40:1704-1712, 2004
3. Body JJ, Diel IJ, Lichinitser M et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with with

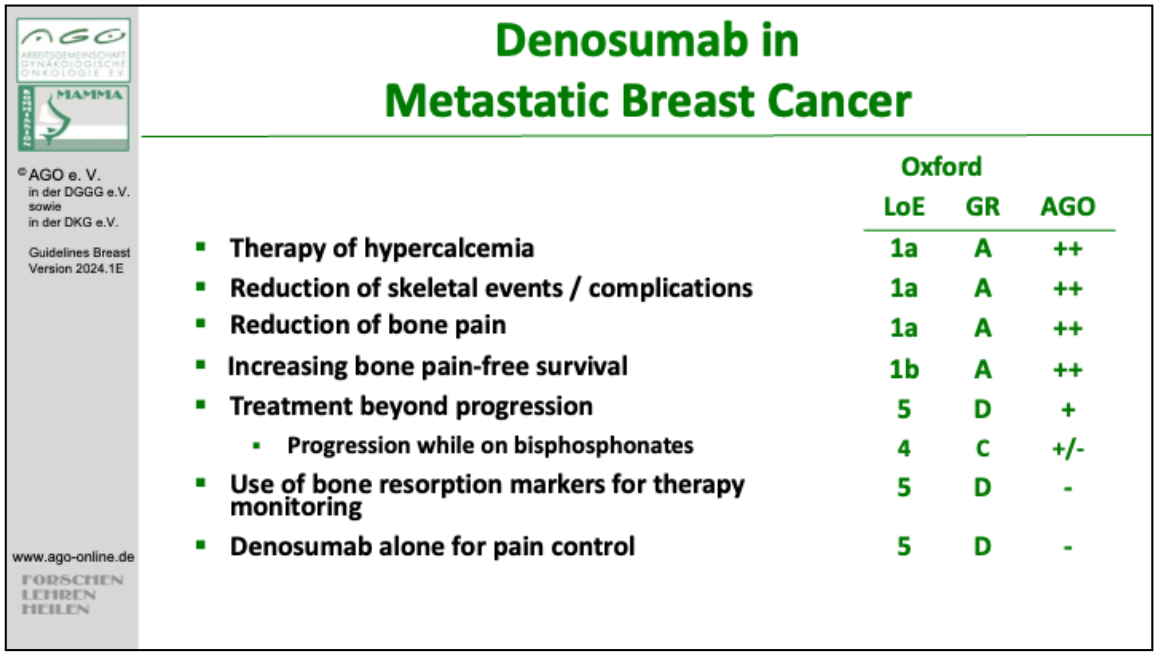
metastatic bone disease; results from two randomized, placebo-controlled phase III studies. Br J Cancer 90:1133-1137., 2004
4. Tripathy D, Lichinitser M, Lazarev A et al. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. Ann Oncol 15:743-750, 2004
5. Rosen LS, Gordon D, Kaminski M et al. . Long-term efficacy and safety of zoledronic acid compared with pamidonate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast cancer. Cancer 98:1735-1744, 2003
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

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017

Bisphosphonates for bone pain control

1. Van Poznak C, Somerfield MR, Barlow W. et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017



Denosumab - Therapy of bone metastases and skeletal related complications

1. Stopeck AT, Lipton A, Body JJ et al. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study, J Clin Oncol 28:5132-5139, 2010
2. Lipton A, Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res 14:6690–6699, 2008
3. Lipton A,Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol *25:*4431–4437, 2007
4. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
5. Tesfamariam Y, Jakob T, Wöckel A et al. Adjuvant bisphosphonates or RANK-ligand inhibitors for patients with breast cancer and bone metastases: A systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2019;137:1-8.

Progression under bisphosphonates

1. Fizazi, K, Lipton, A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 27:1564-71, 2009
2. Mjelstad A, Zakariasson G, Valachis A et al. Optimizing antiresorptive treatment in patients with bone metastases: time to initiation,

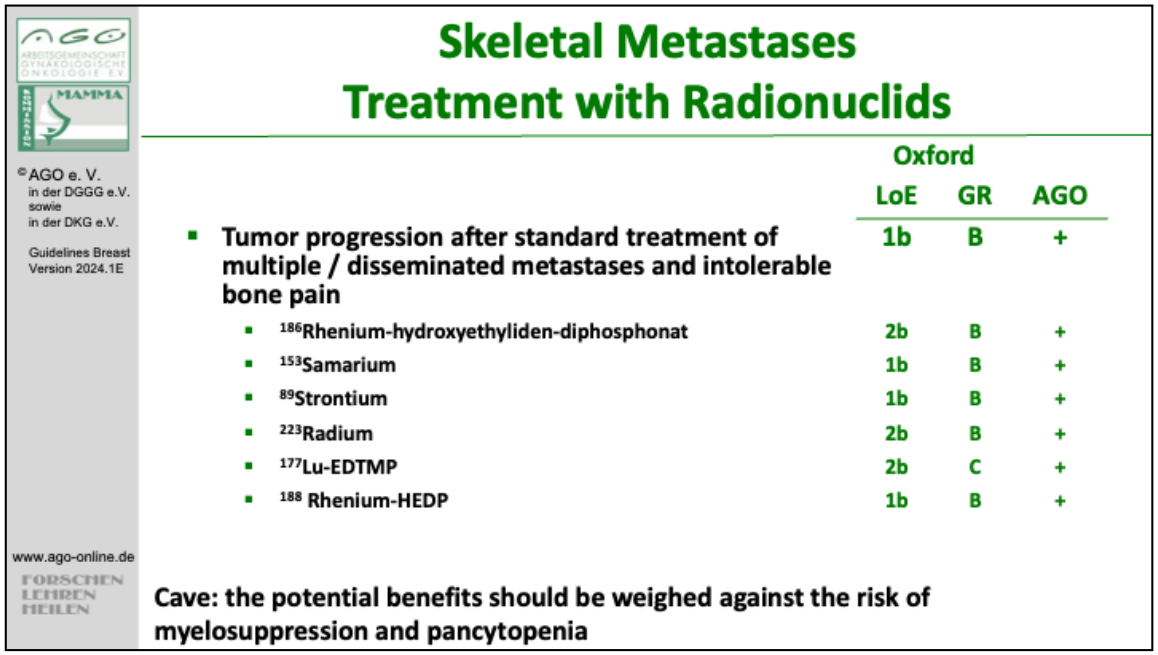
switching strategies, and treatment duration. Support Care Cancer. 2019;27(10):3859-3867. doi: 10.1007/s00520-019-04676-6.

Clinical relevance of bone resorption marker

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017

Bisphosphonates for bone pain control

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017



Reviews / Overview

1. Hoskin PJ: Radioisotopes for metastatic bone pain. Lancet Oncol 6(6):353-4, 2005
2. Bauman G, Chrrette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radioth Oncol 75: 258-70, 2005
3. Roque i Figuls M, Martinez-Zapata MJ, Scott-Brown M et al. Radioisotopes for metastatic bone pain (Cochrane Review). In: The Cochrane Library 2011, Issue 7. John Wiley & Sons, Ltd. Art. No.: CD003347. DOI: 10.1002/14651858.CD003347.pub2

^{186}Rhenium (^{186}Re-HEDP)

1. de Klerk JM, van het Schip AD, Zonnenberg BA et al. Phase 1 study of rhenium-186-HEDP in patients with bone metastases originating from breast cancer. J Nucl Med 137:244-49, 1996
2. Han SH, Zonneberg BA, de Klerk JM et al. 186Re-etidronate in breast cancer patients with metastatic bone pain. J Nucl Med 40:639-42, 1999
3. Kolesnikov-Gauthier H, Carpentier P, Depreux P et al. Evaluation of toxicity and efficacy of 186Re-hydroxyethylidene diphosphonate in patients with painful bone metastases of prostate or breast cancer. J Nucl Med 41:1689-94, 2004
4. Limouris GS, Shukla SK, Condi-Paphiti A et al. Palliative therapy using rhenium-186-HEDP in painful breast osseous metastases. Anticancer Res 17:1767-72, 1997

^{153}Samarium (^{153}Sm-EDTMP)

1. Anderson PM, Wiseman GA, Dispenzieri A et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 20:189-96, 2002
2. Serafini AN. Systemic metabolic radiotherapy with samarium-153 EDTMP for the treatment of painful bone metastasis. Q J Nucl Med. 45:91-9, 2001
3. Kolesnikov-Gauthier H, Lemoine N, Tresch-Bruneel E et al. Efficacy and safety of 153Sm-EDTMP as treatment of painful bone metastasis: a large single-center study. Support Care Cancer. 2017 Sep 17. doi: 10.1007/s00520-017-3885-3

^{89}Strontium (^{89}Sr-Chlorid)

1. Baziotis N, Yakoumakis E, Zissimopoulos A et al. Strontium-89 chloride in the treatment of bone metastases from breast cancer. Oncology 55:377-81, 1998
2. Fuster D, Herranz D, Vidal-Sicart S et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun 21:623-26, 2002
3. Kasalicky J, Krajska V. The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases. Eur J Nucl Med 25:1362-67, 1998
4. Sciuto R, Festa A, Pasqualoni R et al. Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. Breast Cancer Res Treat 66:101-19, 2001

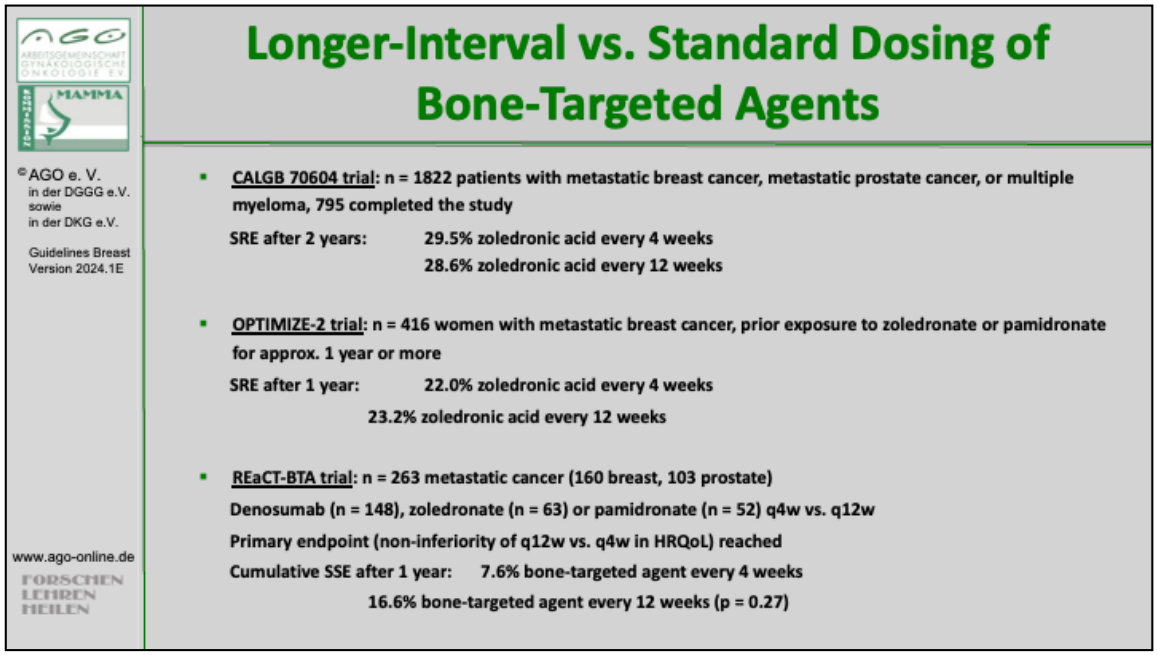
223Ra-dichloride:

1. Pandit-Taskar N, Larson SM, Carrasquillo JA. Bone-seeking radiopharmaceuticals for treatment of osseous metastases, Part 1: α therapy with 223Ra-dichloride. J Nucl Med 55(2):268-74, 2015
2. Rugo HS, Van Poznak CH, Neven P et al. Radium-223 in women with hormone receptor-positive bone-metastatic breast cancer receiving endocrine therapy: pooled analysis of two international, phase 2, randomized, double-blind, placebo-controlled trials. Breast Cancer Res Treat 2023 Dec 20. Doi: 10.1007/s10549-023-07147-z.

177Lu (Lutetium)-EDTMP

1. Agarwal KK, Singla S, Arora G, Bal C. (177)Lu-EDTMP for palliation of pain from bone metastases in patients with prostate and breast cancer: a phase II study. Eur J Nucl Med Mol Imaging. 42(1):79-88,2015

2. Sharma S, Singh B, Koul A et al. Comparative Therapeutic Efficacy of 153Sm-EDTMP and 177Lu-EDTMP for Bone Pain Palliation in Patients with Skeletal Metastases: Patients' Pain Score Analysis and Personalized Dosimetry. Front Med (Lausanne). 2017 May 1;4:46. doi: 0.3389/fmed.2017.00046. eCollection 2017.



Randomized trials – Zoledronic acid:

1. CALGB 70604: 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
2. OPTIMIZE-2: Hortobagyi GN, Van Poznak C, Harker WG et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 3(7):906-912, 2017
3. Amadori D, Aglietta M, Alessi B et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 14(7):663-70, 2013

Randomized trials – Other bone-targeted agents

1. REaCT-BTA: Clemons M, Ong M, Stober C et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer 2021; 142: 132-140
2. Amir E, Freedman O, Carlsson L et al. Randomized Feasibility Study of De-escalated (Every 12 wk) Versus Standard (Every 3 to 4 wk) Intravenous Pamidronate in Women With Low-risk Bone Metastases From Breast Cancer. Am J Clin Oncol 2013; 36: 436-442
3. Lipton A, Steger GG, Figueroa J et al. Randomized Active-Controlled Phase II Study of Denosumab Efficacy and Safety in Patients With

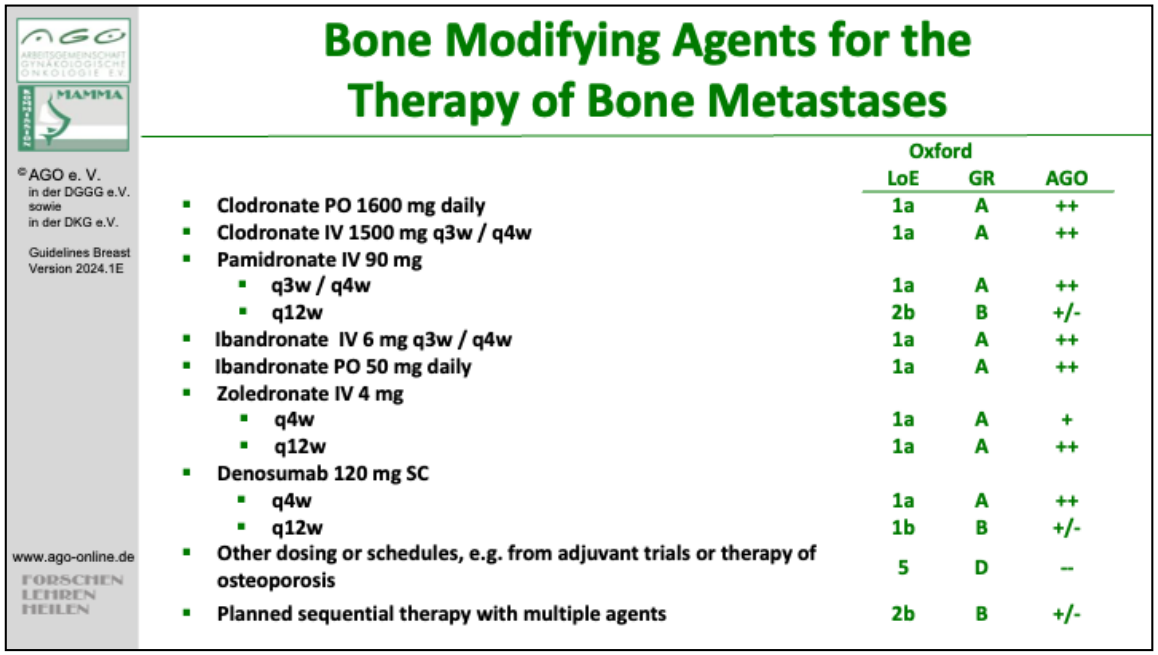
Breast Cancer-Related Bone Metastases. J Clin Onc 2007: 25 (28): 4431-4437

Non-randomized studies:

1. Addison CL, Bouganim N, Hilton J et al. A phase II, multicentre trial evaluating the efficacy of de-escalated bisphosphonate therapy in metastatic breast cancer patients at low-risk of skeletal-related events. Breast Cancer Res Treat 2014; 144: 615-624

Systematic reviews:

1. Awan AA, Hutton B, Hilton J et al., De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2019;176(3):507-517.



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	+/-

Reviews / Guidelines:

1. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
2. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017
3. Ibrahim MF, Mazzarello S, Shorr R et al. Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis. Ann Oncol. 26(11):2205-13, 2015
4. Awan AA, Hutton B, Hilton J et al., De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2019;176(3):507-517.
5. Shapiro CL, Moriarty JP, Dusetzina S et al. Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance). J Clin Oncol. 2017; 35(35):3949-3955.

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
2. Hortobagyi GN, Van Poznak C, Harker WG et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 3(7):906-912, 2017
3. Amadori D, Aglietta M, Alessi B et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 14(7):663-70, 2013
4. Santini D, Galvano A, Pantano F et al. How do skeletal morbidity rate and special toxicities affect 12-week versus 4-week schedule zoledronic acid efficacy? A systematic review and a meta-analysis of randomized trials. Crit Rev Oncol Hematol. 2019;142:68-75.

Pamidronate:

1. Amir E, Freedman O, Carlsson L et al. Randomized Feasibility Study of De-escalated (Every 12 wk) Versus Standard (Every 3 to 4 wk) Intravenous Pamidronate in Women With Low-risk Bone Metastases From Breast Cancer. Am J Clin Oncol 2013; 36: 436-442
2. Addison CL, Bouganim N, Hilton J et al. A phase II, multicentre trial evaluating the efficacy of de-escalated bisphosphonate therapy in metastatic breast cancer patients at low-risk of skeletal-related events. Breast Cancer Res Treat 2014; 144: 615-624

Denosumab & bisphosphonates:

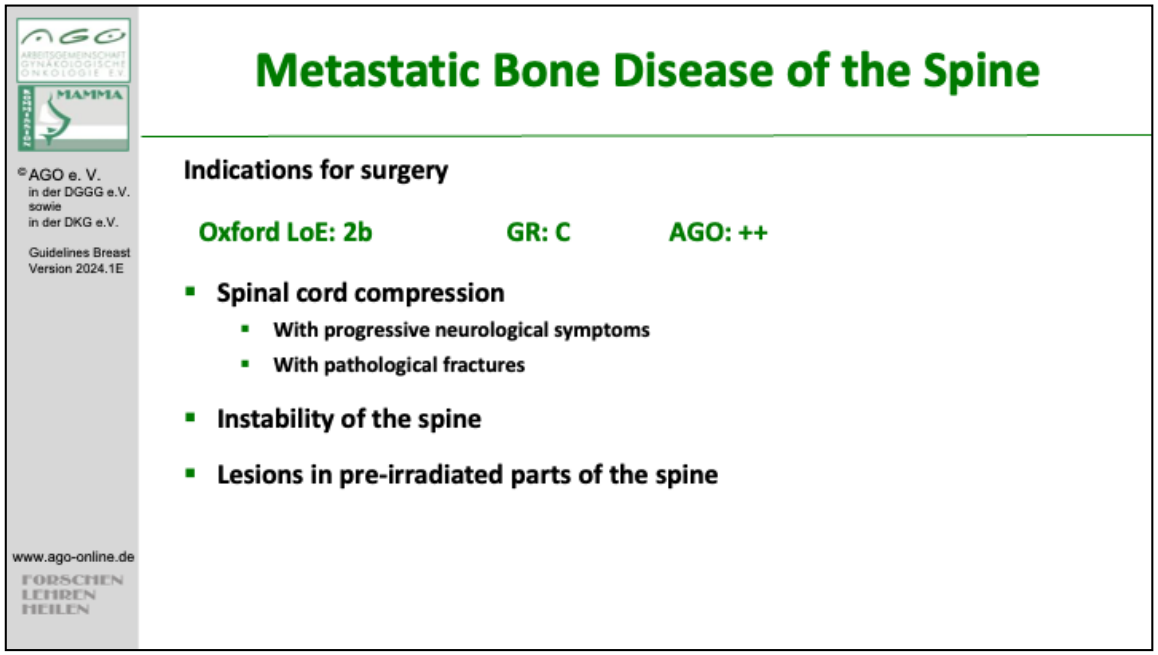
1. Clemons M, Ong M, Stober C et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer 2021; 142: 132-140
2. Lipton A, Steger GG, Figueroa J et al. Randomized Active-Controlled Phase II Study of Denosumab Efficacy and Safety in Patients With Breast Cancer-Related Bone Metastases. J Clin Onc 2007: 25 (28): 4431-4437
3. Clemons M, Liu M, Stober C, Pond G, et al.; REaCT investigators. Two-year results of a randomised trial comparing 4- versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. J Bone Oncol. 2021 Sep 2;30:100388. doi: 10.1016/j.jbo.2021.100388. PMID: 34567960; PMCID: PMC8449269.

Denosumab:

1. Templeton AJ, Stalder L, Bernhard J et al. Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: A noninferiority phase III trial (SAKK 96/12, REDUSE). J Clin Oncol 32:5s, 2014 (suppl; abstr TPS5095)

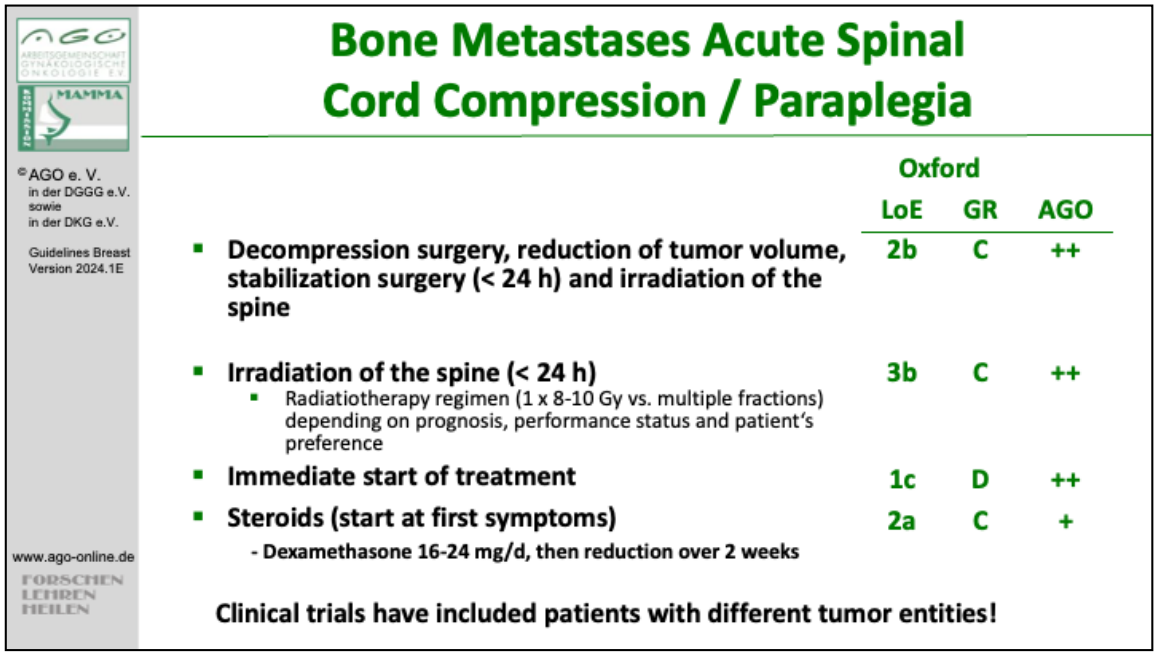
Sequential therapy with different BTAs:

1. Srivastava A, Nogueras Gonzales GM, Geng Y et al. Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. Support Care Cancer. 2020. doi: 10.1007/s00520-020-05882-3.



1. Wood TJ, Racano A, Yeung H et al. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 21(13):4081-9, 2014
2. Ju DG, Yurter A, Gokaslan ZL et al. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 10;5(3):263-71, 2014
3. Rades D, Veninga T, Stalpers LJ et al. Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. Int J Radiat Oncol Biol Phys 64(1):182-8, 2006
4. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine: evaluation and treatment. Clin Orthop 2003;415 Suppl:S165-75
5. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
6. Ahangar P, Aziz M, Rosenzweig DH et al. Advances in personalized treatment of metastatic spine disease. Ann Transl Med. 2019;7(10):223. Review.
7. Conti A, Acker G, Kluge A et al., Decision Making in Patients With Metastatic Spine. The Role of Minimally Invasive Treatment Modalities. Front Oncol. 2019:19;9:915.

8. Schoenfeld AJ, Le HV, Marjoua Y et al. Assessing the utility of a clinical prediction score regarding 30-day morbidity and mortality following metastatic spinal surgery: the New England Spinal Metastasis Score (NESMS). Spine J. 2016;16(4):482-90, doi: 10.1016/j.spinee.2015.09.043
9. Rothrock RJ, Barzilai O, Reiner AS et al. Survival Trends After Surgery for Spinal Metastatic Tumors: 20-Year Cancer Center Experience. Neurosurgery 2020;nyaa380, doi: 10.1093/neuros/nyaa380.



Recommendations and Clinical Practice Guidelines:

1. Loblaw DA, Mitera G, Ford M et al. A 2011 Updated Systematic Review and Clinical Practice Guideline for the Management of Malignant Extradural Spinal Cord Compression. Int J Radiat Oncol Biol Phys. 2012;84(2):312-7. doi: 10.1016/j.ijrobp.2012.01.014.
2. Souchon R, Feyer P, Thomssen C et al. Clinical recommendations of DEGRO and AGO on preferred standard palliative radiotherapy (RT) of bone and cerebral metastases, metastatic spinal cord compression, and leptomeningeal carcinomatosis in breast cancer. Breast Care 5:401-7 , 2010
3. Souchon R, Wenz F, Sedlmayer F et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 185:417-424, 2009
4. Groenen KHJ, van der Linden YM, Brouwer T et al. The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management. Cancer Treat Rev 2018;69:29-38. doi: 10.1016/j.ctrv.2018.05.013.
5. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf

Reviews:

1. Loblaw A, George KJ, Misra V. Surgical and Radiotherapeutic Management of Malignant Extradural Spinal Cord Compression. Clin Oncol (R Coll Radiol) 2020;32(11):745-752. doi: 10.1016/j.clon.2020.07.022.

Operative therapy:

1. Patchell RA, Tibbs PA, Regine WF et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005 Aug 20-26;366(9486):643-8, doi: 10.1016/S0140-6736(05)66954-1.
2. Yang XG, Lun DX, Hu YC et al. Prognostic effect of factors involved in revised Tokuhashi score system for patients with spinal metastases: a systematic review and Meta-analysis. BMC Cancer 2018;18(1):1248. doi: 10.1186/s12885-018-5139-2.
3. Alpantaki K, Ioannidis A, Raptis K et al. Surgery for spinal metastatic tumors: Prognostication systems in clinical practice (Review). Mol Clin Oncol. 2020;12(5):399-402, doi: 10.3892/mco.2020.2008

Radiation therapy: Randomized studies:

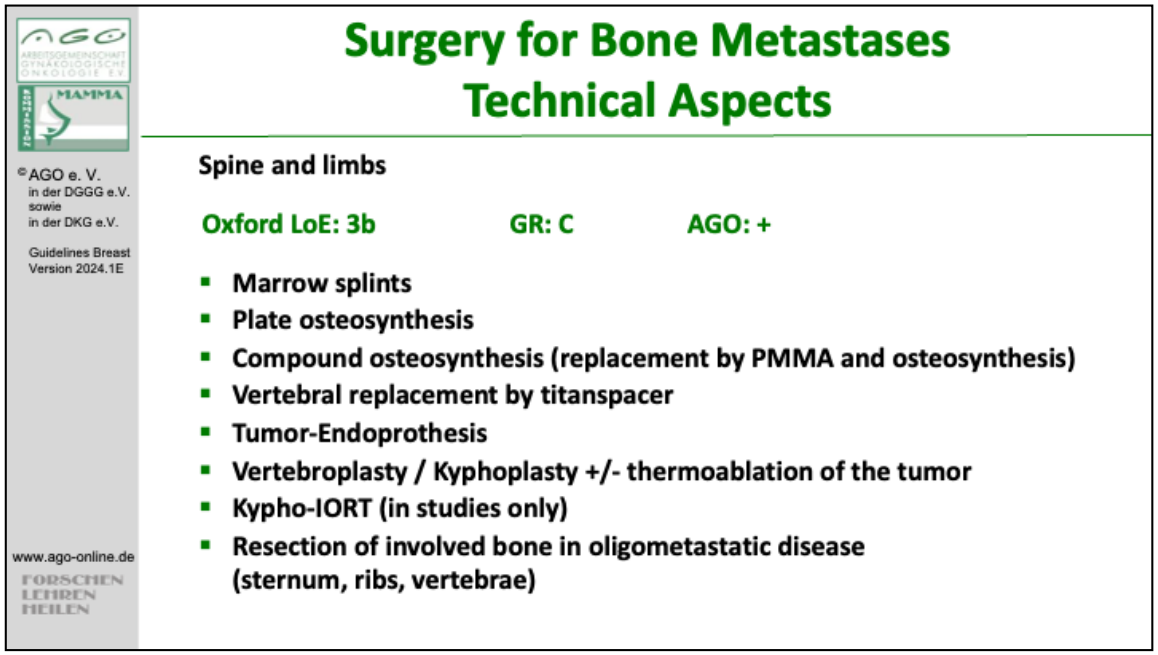
1. Hoskin PJ, Hopkins K, Misra V et al. Effect of Single-Fraction vs Multifraction Radiotherapy on Ambulatory Status Among Patients With Spinal Canal Compression From Metastatic Cancer: The SCORAD Randomized Clinical Trial. JAMA 2019;322(21):2084-2094, doi: 10.1001/jama.2019.17913.
2. Rades D, Segedin B, Conde-Moreno AJ et al. Radiotherapy With 4 Gy x 5 Versus 3 Gy x 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)
3. Thirion PG, Dunne MT, Kelly PJ et al. Non-inferiority randomised phase 3 trial comparing two radiation schedules (single vs. five fractions) in malignant spinal cord compression. Br J Cancer. 2020;122(9):1315-1323. doi: 10.1038/s41416-020-0768-z
4. Maranzano E, Bellavita R, Rossi R et al. Short-Course Versus Split-Course Radiotherapy in Metastatic Spinal Cord Compression: Results of a Phase III, Randomized, Multicenter Trial. J Clin Oncol. 2005;23(15):3358-65. doi: 10.1200/JCO.2005.08.193.
5. Maranzano E, Trippa F, Casale M et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiother Oncol. 2009;93(2):174-9, doi: 10.1016/j.radonc.2009.05.012.

Radiation therapy: Non-randomized studies:

1. Rades D, Cacicedo J, Conde-Moreno AJ et al. Precision Radiation Therapy for Metastatic Spinal Cord Compression: Final Results of the PRE-MODE Trial. Int J Radiat Oncol Biol Phys 2020;106(4):780-789. doi: 10.1016/j.ijrobp.2019.11.401.
2. Rades D, Conde-Moreno AJ, Cacicedo J et al. 1x8 Gy versus 5x4 Gy for metastatic epidural spinal cord compression: a matched-pair study of three prognostic patient subgroups. Radiat Oncol 2018;13(1):21. doi: 10.1186/s13014-018-0968-3.
3. Rades D, Lange M, Veninga T et al. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2011;79(2):524-30
4. Rades D, Karstens JH, Hoskin PJ, et al. Escalation of radiation dose beyond 30 Gy in 10 fractions for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 67:525-31, 2007
5. Rades D, Heidenreich E, Karstens JH. Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 53:975-9, 2002

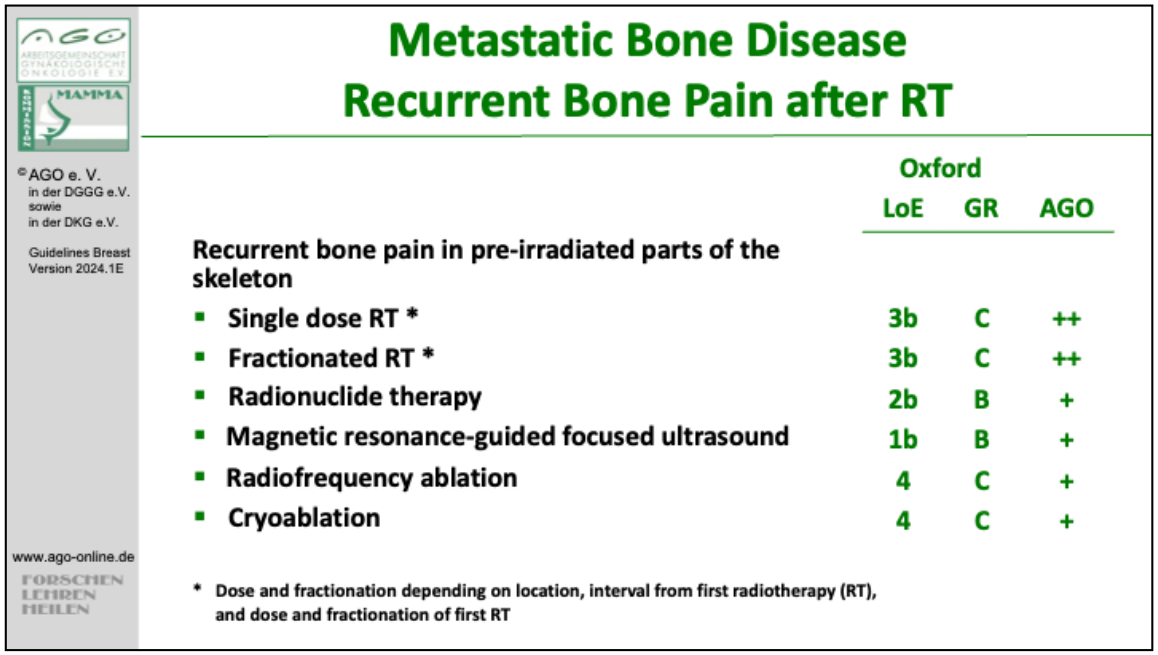
Steroids: Systematic review:

1. Kumar A, Weber MH, Gokaslan Z et al. Metastatic Spinal Cord Compression and Steroid Treatment A Systematic Review. Clin Spine Surg. 2017;30(4):156-163. doi: 10.1097/BSD.0000000000000528.



1. Ju DG, Yurter A, Gokaslan ZL et al. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 10;5(3):263-71, 2014
2. Wood TJ, Racano A, Yeung H et al. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 21(13):4081-9, 2014
3. Ali SM, Harvey HA, Lipton A: Metastatic breast cancer: overview of treatment. Clin Orthop Rel Res 2003;1 (415S) (Suppl): 132–137
4. Fourney DR, Gokaslan ZL: Thoracolumbar spine: surgical treatment of metastatic disease. Curr Opin Orthop 14 (3): 144–152, 2013
5. Fourney DR, Schomer DF, Nader R et al: Percutaneous and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 98 (Suppl): 21–30, 2003
6. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine. Evaluation and treatment. Clin Orthop Rel Res (415S) (Suppl): 165–175, 2003
7. Berenson J1, Pflugmacher R, Jarzem P et al. Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 12(3):225-35, 2011
8. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf

9. Bludau F, Winter L, Welzel G et al. Long-term outcome after combined kyphoplasty and intraoperative radiotherapy (Kypho-IORT) for vertebral tumors. Radiat Oncol 2020; 15: 263



Recurrent bone pain in pre-irradiated parts of the skeleton

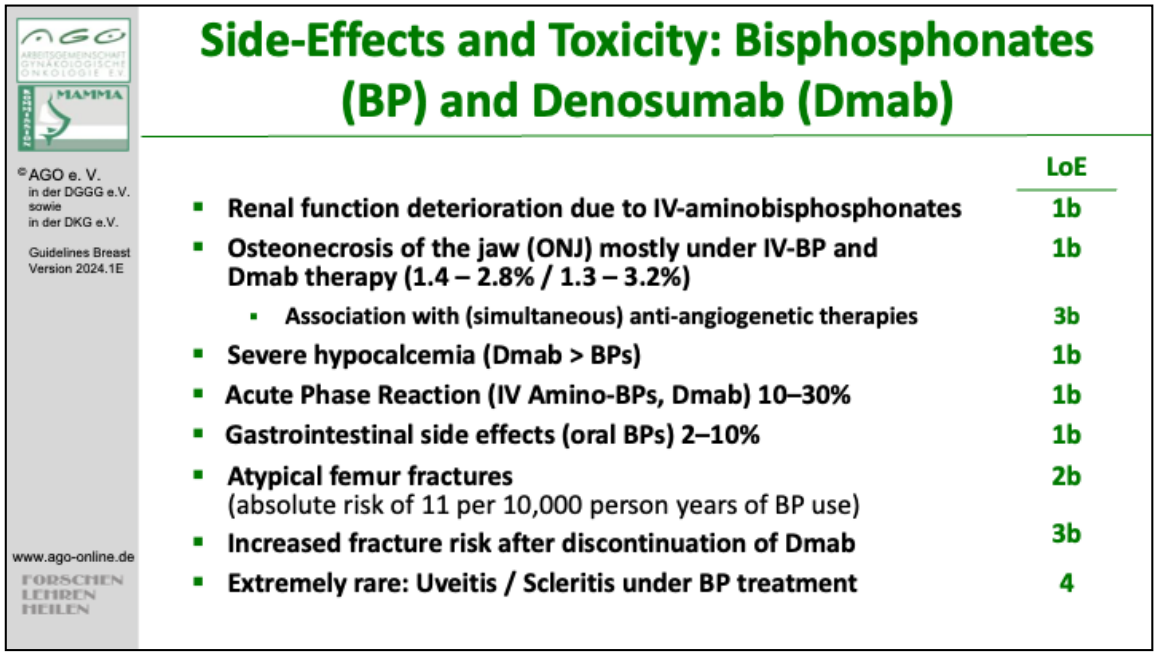
1. Souchon R, Wenz F, Sedlmayer F et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 185:417-424, 2009
2. Souchon R, Feyer P, Thomssen C et al. Clinical recommendations of DEGRO and AGO on preferred standard palliative radiotherapy (RT) of bone and cerebral metastases, metastatic spinal cord compression, and leptomeningeal carcinomatosis in breast cancer. Breast Care 5:401-7, 2010
3. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
4. Chow E, Meyer RM, Chen BE et al. Impact of reirradiation of painful osseous metastases on quality of life and function: a secondary analysis of the NCIC CTG SC.20 randomized trial. J Clin Oncol. 2014;32(34):3867-73. doi: 10.1200/JCO.2014.57.6264.

Magnetic resonance-guided focused ultrasound

1. Hurwitz MD, Ghanouni P, Kanaev SV, et al. Magnetic resonance-guided focused ultrasound for patients with painful bone metastases: phase III trial results. J Natl Cancer Inst 2014; 106.

Cryoablation / Radiofrequency ablation

1. Dechamps F, Farouil G, Ternes N et al.: Thermal ablation techniques: a curative treatment of bone metastases in selected patients? Eur Radiol 24(8):1971-80, 2014
2. Hegg RM, Kurup AN, Schmit GD et al.: Cryoablation of sternal metastases for pain palliation and local tumor control. J Vasc Interv Radiol 25(11):1665-70, 2014
3. De Marini P, Cazzato RL, Auloge P et al. Percutaneous image-guided thermal ablation of bone metastases: a retrospective propensity study comparing the safety profile of radio-frequency ablation and cryo-ablation. Int J Hyperthermia 2020;37(1):1386-1394. doi: 10.1080/02656736.2020.1859628.



Bisphosphonates

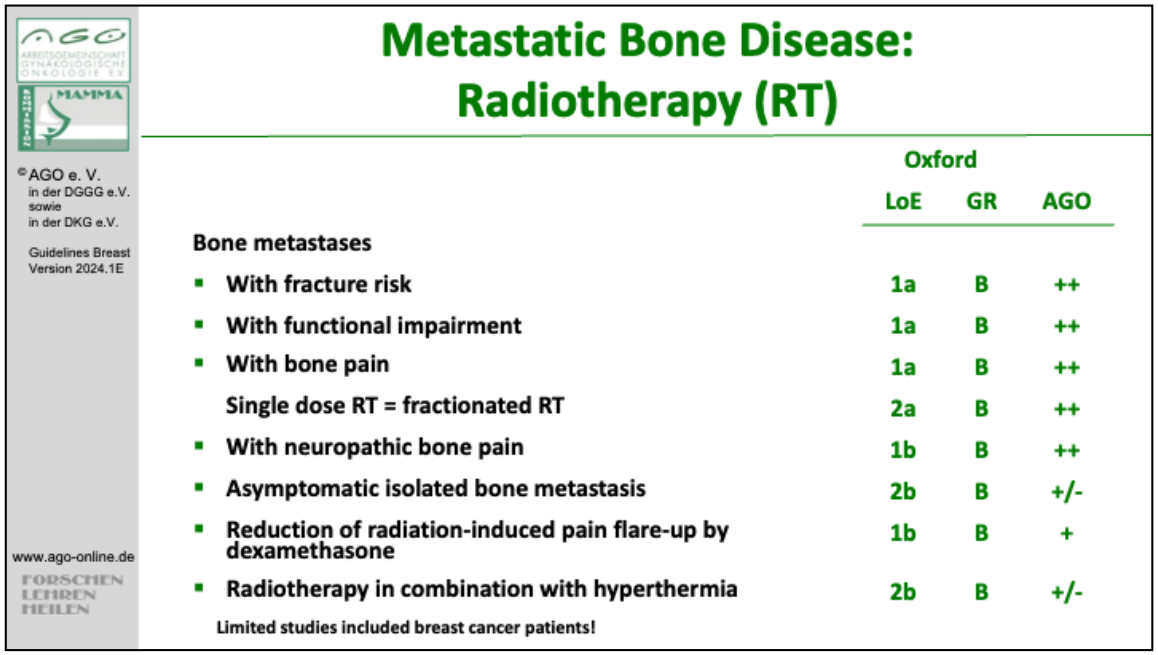
1. Schilcher, J., V. Koeppen, P. Aspenberg et al. Risk of atypical femoral fracture during and after bisphosphonate use. Acta Orthop 100-107, 2015
2. Body JJ. Breast Cancer: Bisphosphonate therapy for metastatic bone disease. Clin Cancer Res. 2006; 12(20 Suppl):6258s-6263s.
3. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer 98(11):1736-40., 2008
4. Dunstan CR, Felsenberg D, Seibel MJ. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. Nat Clin Pract Oncol 4(1):42-55, 2007
5. Tralongo, P, Repetto, L, Di Mari, A, et al. Safety of long-term administration of bisphosphonates in elderly cancer patients. Oncology 67:11216, 2004
6. Chang, JT, Green, L, Beitz, J. Renal failure with the use of zoledronic acid. N Engl J Med 349(17):1676-9, 2003
7. Hillner BE, Ingle JN, Chlebowski RT et al. American Society of Clinical Oncology: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21(21):4042-57, 2003
8. Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 19(3):420-32, 2008
9. Clark EM, Durup D: Inflammatory eye reactions with bisphosphonates and other osteoporosis medications: What are the risks? Ther Adv Musculoskelet Dis 7:11-16, 2015.

Denosumab

1. Stopeck AT et al. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study, J Clin Oncol 28:5132-5139, 2010
2. Taylor KH, Middlefell LS, and Mizen KD, "Osteonecrosis of the Jaws Induced by Anti-RANK Ligand Therapy," Br J Oral Maxillofac Surg 48(3):221-3, 2010
3. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31: 1650-1663.
4. Wang R, Rajanayagam S, Ngan J et al. Incidence of post-denosumab rebound hypercalcaemia in bony-metastatic breast cancer. Calcif Tissue Int 2022; 111: 391-395.

Sequential therapy

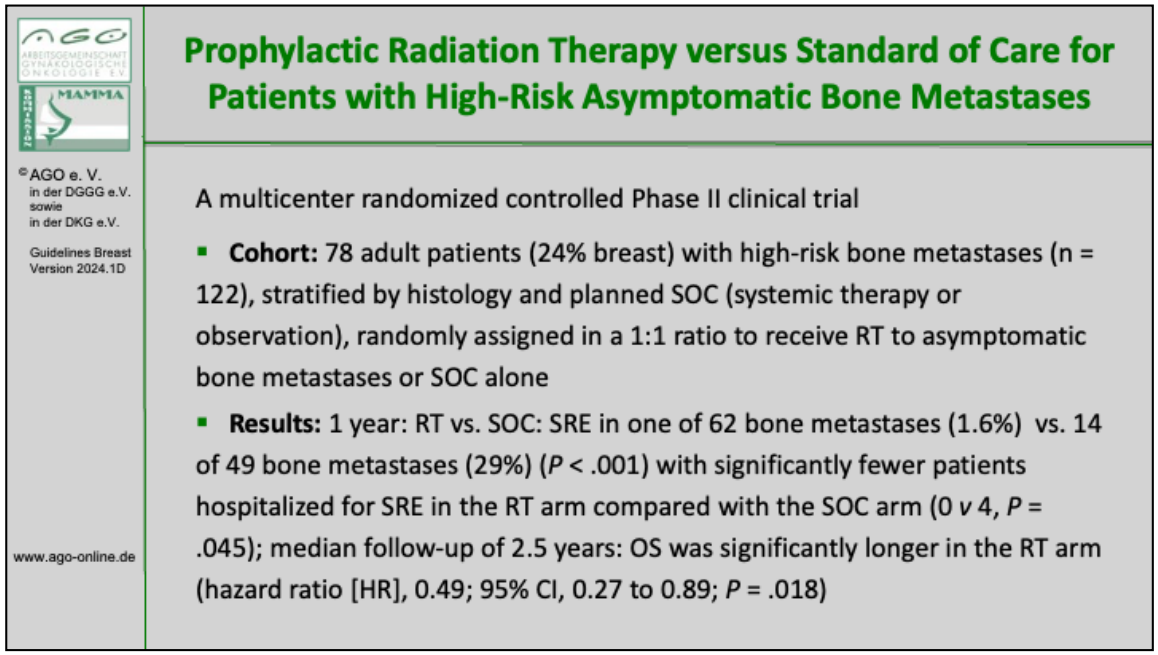
1. Srivastava et al., Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. Support Care Cancer. 2020 Nov 15. doi: 10.1007/s00520-020-05882-3. Online ahead of print.



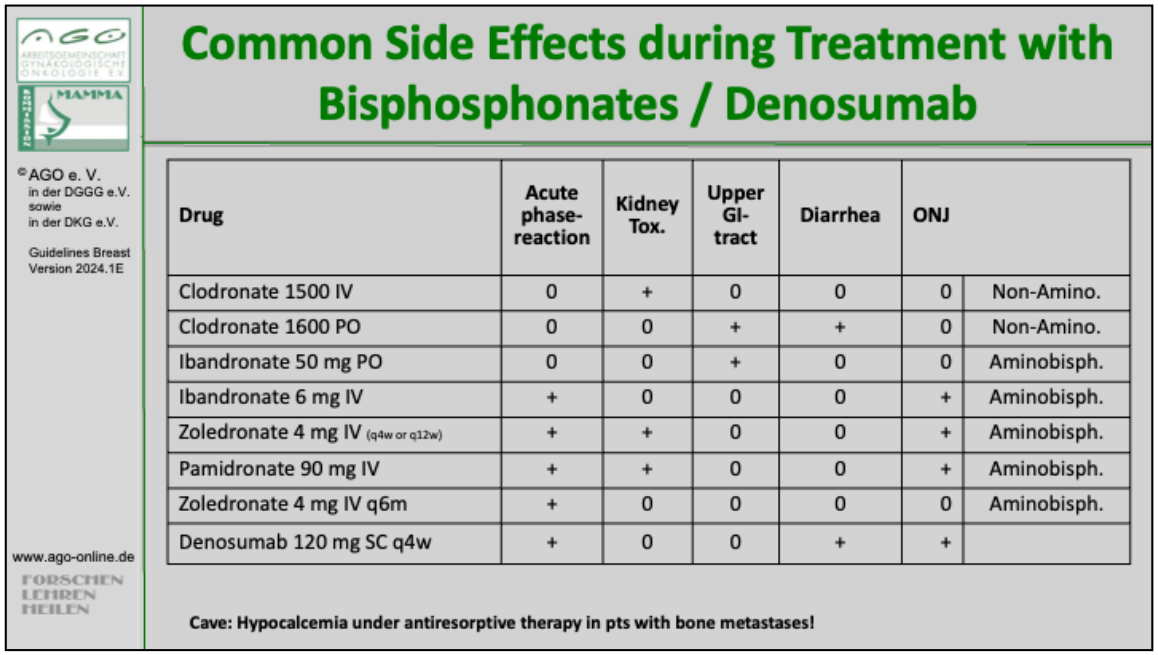
1. Souchon R, Feyer P, Thomssen C et al. Clinical recommendations of DEGRO and AGO on preferred standard palliative radiotherapy (RT) of bone and cerebral metastases, metastatic spinal cord compression, and leptomeningeal carcinomatosis in breast cancer. Breast Care 5:401-7, 2010
2. Souchon R, Wenz F, Sedlmayer F, Budach W et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 185:417-424, 2009
3. Hartsell WF, Scott CB, Bruner DW et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst. 2005;97(11):798-804. doi: 10.1093/jnci/dji139.
4. McDonald R, Ding K, Brundage M et al. Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol 3(7):953-959, 2017
5. Lutz S, Balboni T, Jones J et al. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017;7(1):4-12. doi: 10.1016/j.prro.2016.08.001
6. McQuay HJ, Collins SL, Carroll D et al. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev 2000;2:CD001793
7. Chow R, Hoskin P, Hollenberg D et al. Efficacy of single fraction conventional radiation therapy for painful uncomplicated bone metastases: a systematic review and meta-analysis. Ann Palliat Med. 2017;6(2):125-142. doi: 10.21037/apm.2016.12.04.
8. Chow E, Meyer RM, Ding K et al. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for

bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial. Lancet Oncol 16(15):1463-72, 2015

9. Chi MS, Yang KL, Chang YC et al. Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial. Int J Radiat Oncol Biol Phys 100(1):78-87, 2018
10. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
11. Pin Y, Paix A, Le Fevre C et al. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. Crit Rev Oncol Hematol. 2018;123:132-137. doi: 10.1016/j.critrevonc.2018.01.006.
12. Gillespie EF, Yang JC, Mathis NJ et al. Prophylactic radiation therapy versus standard of care for patients with high-risk asymptomatic bone metastases: a multicenter, randomized phase II clinical trial. J Clin Oncol 2024; 42: 38-46.



1. Gillespie EF, Yang JC, Mathis NJ, et al. Prophylactic Radiation Therapy Versus Standard of Care for Patients With High-Risk Asymptomatic Bone Metastases: A Multicenter, Randomized Phase II Clinical Trial. *J Clin Oncol*. 2024;42(1):38-46. doi:10.1200/JCO.23.00753



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3. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer 98(11):1736-40., 2008
4. Dunstan CR, Felsenberg D, Seibel MJ. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. Nat Clin Pract Oncol 4(1):42-55, 2007
5. Tralongo, P, Repetto, L, Di Mari, A, et al. Safety of long-term administration of bisphosphonates in elderly cancer patients. Oncology 67:11216, 2004
6. Chang, JT, Green, L, Beitz, J. Renal failure with the use of zoledronic acid. N Engl J Med 349(17):1676-9, 2003
7. Hillner BE, Ingle JN, Chlebowski RT et al. American Society of Clinical Oncology: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21(21):4042-57, 2003
8. Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 19(3):420-32, 2008
9. Clark EM, Durup D: Inflammatory eye reactions with bisphosphonates and other osteoporosis medications: What are the risks? Ther Adv Musculoskelet Dis 7:11-16, 2015

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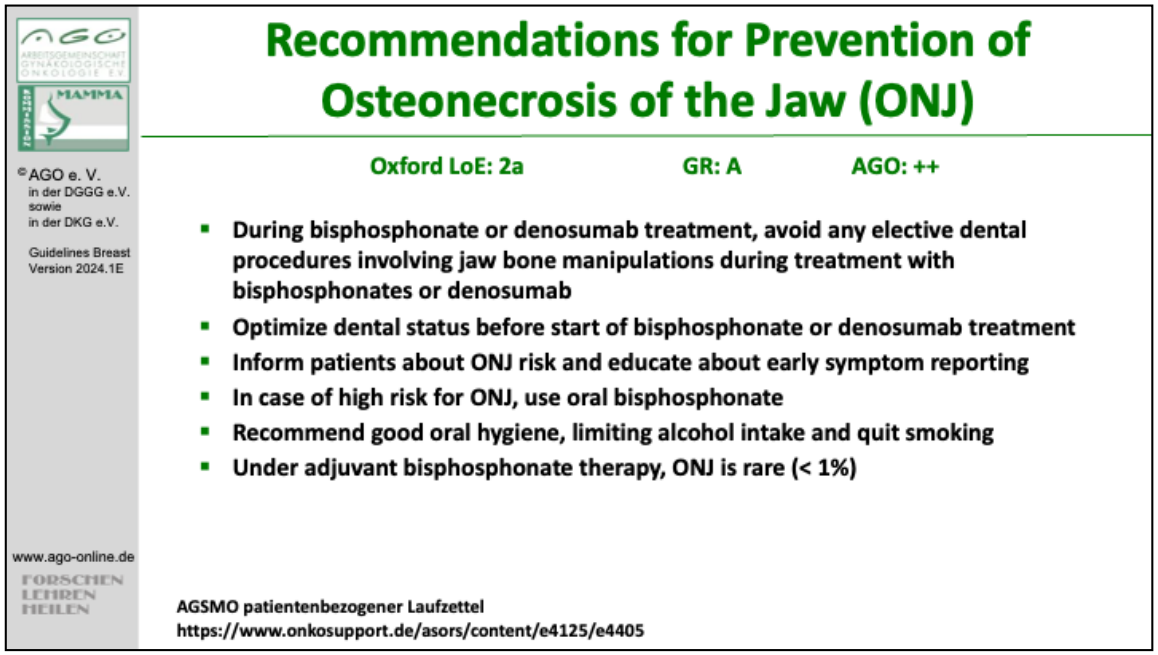
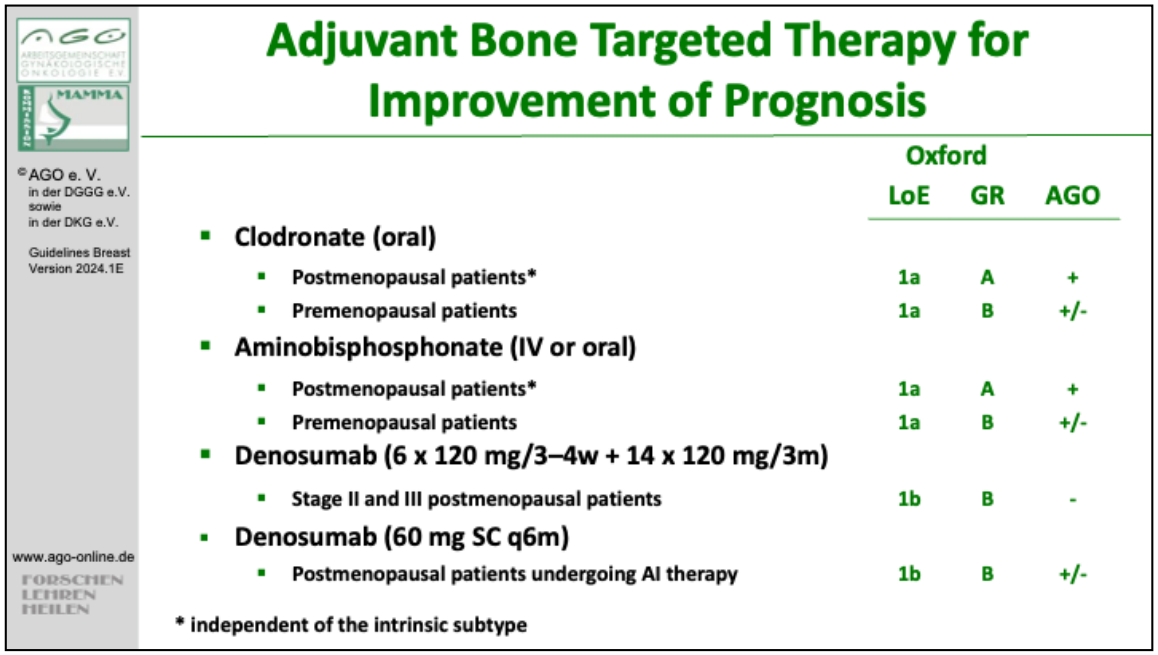
1. Stopeck AT et al. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study, J Clin Oncol 28:5132-5139, 2010
2. Taylor KH, Middlefell LS, and Mizen KD, "Osteonecrosis of the Jaws Induced by Anti-RANK Ligand Therapy," Br J Oral Maxillofac Surg 48(3):221-3, 2010



1. Izzotti A, Menini M, Pulliero A et al. Biphosphonates-associated osteonecrosis of the jaw: the role of gene-environment interaction. J Prev Med Hyg 54(3): 138-145, 2013
2. Fehm T, Felsenberg D, Krimmel M et al. Bisphosphonate-associated osteonecrosis of the jaw in breast cancer patients: recommendations for prevention and treatment. Breast 18(4):213-7, 2009
3. Khan AA, Sándor GK, Dore E et al. Canadian Association of Oral and Maxillofacial Surgeons. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 35(7):1391-7, 2008
4. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons.American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 65(3):369-76, 2007
5. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35(18):2062-2081, 2017
6. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
7. Yarom N, Shapiro CL, Peterson DE et al Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline.

J Clin Oncol. 2019: 37(25):2270-2290. doi: 10.1200/JCO.19.01186.

8. S3-Guideline: Antiresorptiva-assoziierte Kiefernekrose (AR-ONJ) AWMF Register Nr 007 – 091, Stand: 02.12.2018 , gültig bis 01.12.2023; https://www.awmf.org/uploads/tx_szleitlinien/007-091l_S3_Antiresorptiva-assoziierte-Kiefernekrosen-AR-ONJ_2018-12.pdf
9. https://www.onkosupport.de/asors/content/e4125/e4405



Clodronate

1. Ben-Aharon I, Vidal L, Rizel S et al. Bisphosphonates in the adjuvant setting of breast cancer therapy--effect on survival: a systematic review and meta-analysis. PLoS One. 2013 Aug 26;8(8):e70044. doi: 10.1371/journal.pone.0070044. eCollection 2013. Review.
2. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer: an Overview. Clin Oncol 25:135-45, 2013
3. Zhu J, Zheng Y, Zhou Z. Oral adjuvant clodronate therapy could improve overall survival in early breast cancer. Results from an updated systematic review and meta-analysis. Eur J Cancer 49:2086-92, 2013
4. Diel IJ, Jaschke A, Solomayer EF et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow—a long-term follow-up. Ann Oncol 19: 2007-2011, 2008
5. Powles TJ, McCloskey E, Paterson AH et al. Oral clodronate and reduction in loss of bone mineral density in women with operable breast cancer. J Natl Cancer Inst 90:704-8, 1998
6. Saarto T, Vehmanen L, Virkkunen P et al. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. Acta Oncol 43(7):650-656, 2004
7. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.

Adjuvant Aminobisphosphonates

1. Ben-Aharon I, Vidal L, Rizel S et al. Bisphosphonates in the adjuvant setting of breast cancer therapy--effect on survival: a systematic review and meta-analysis. PLoS One. 2013 Aug 26;8(8):e70044. doi: 10.1371/journal.pone.0070044. eCollection 2013. Review.
2. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer: an Overview. Clin Oncol 25:135-45, 2013
3. Valachis A, Polyzos NP, Coleman RE et al. Adjuvant therapy with zoledronic acid in patients with breast cancer. A systematic review and meta-analysis. The Oncologist 18:353-61, 2013
4. Coleman RE, Thorpe HC, Cameron D et al. Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04). 33. SABCS 2010, S4-5.
5. Brufsky AM, Bosserman LD, Caradonna RR et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. Clin Breast Cancer 9(2):77-85, 2009
6. Eidtmann H, de Boer R, Bundred N et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Ann Oncol 21(11):2188-94, 2010
7. Hadji P, Coleman RE, Wilson C et al. Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice from a European Panel. Ann Oncol. 2015 Dec 17. pii: mdv617.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 3;386(10001):1353-61, 2015
9. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
10. Friedl TWP, Fehm T, Müller V et al. Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Aug 1;7(8):1149-1157. doi: 0.1001/jamaoncol.2021.1854.PMID: 34165508

Denosumab

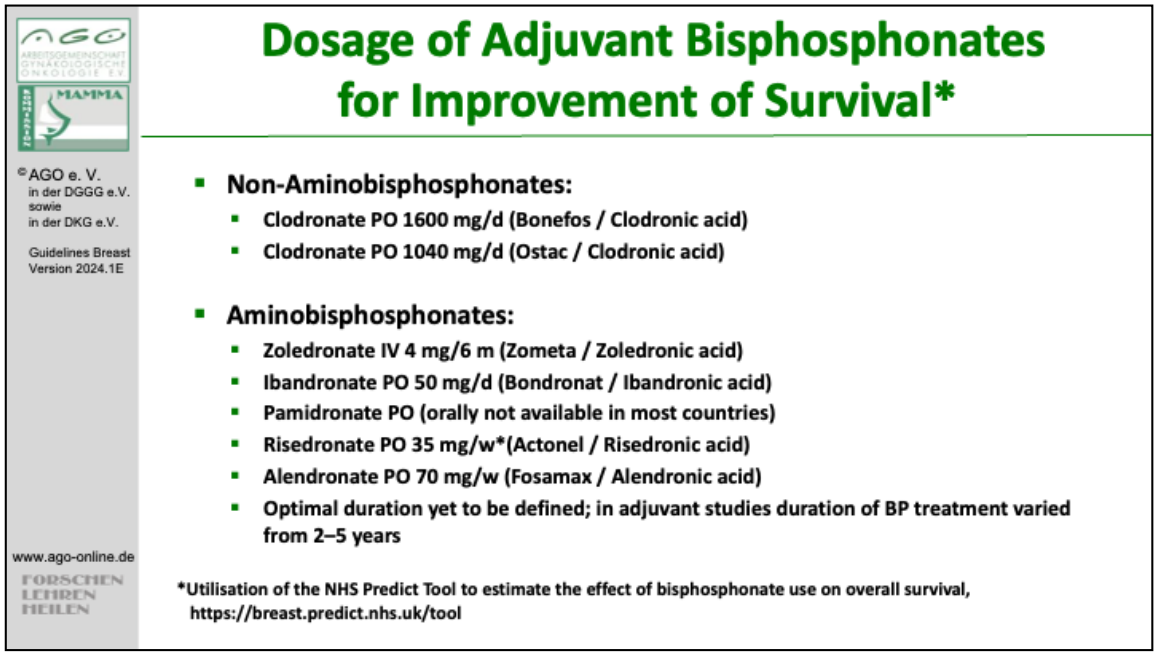
1. Gnant M, Pfeiler G, Steger GG, Austrian Breast and Colorectal Cancer Study Group. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Mar;20(3):339-351.
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)

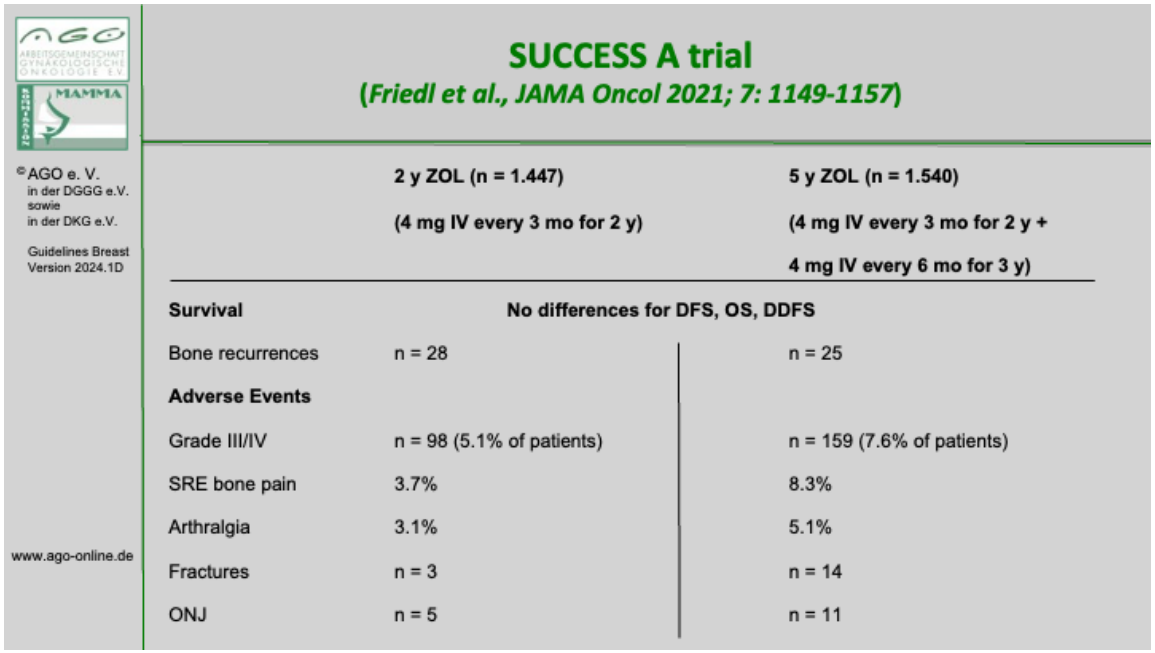
3. Coleman R, Finkelstein DM, Barrios C et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020 21(1):60-72.

Guidelines

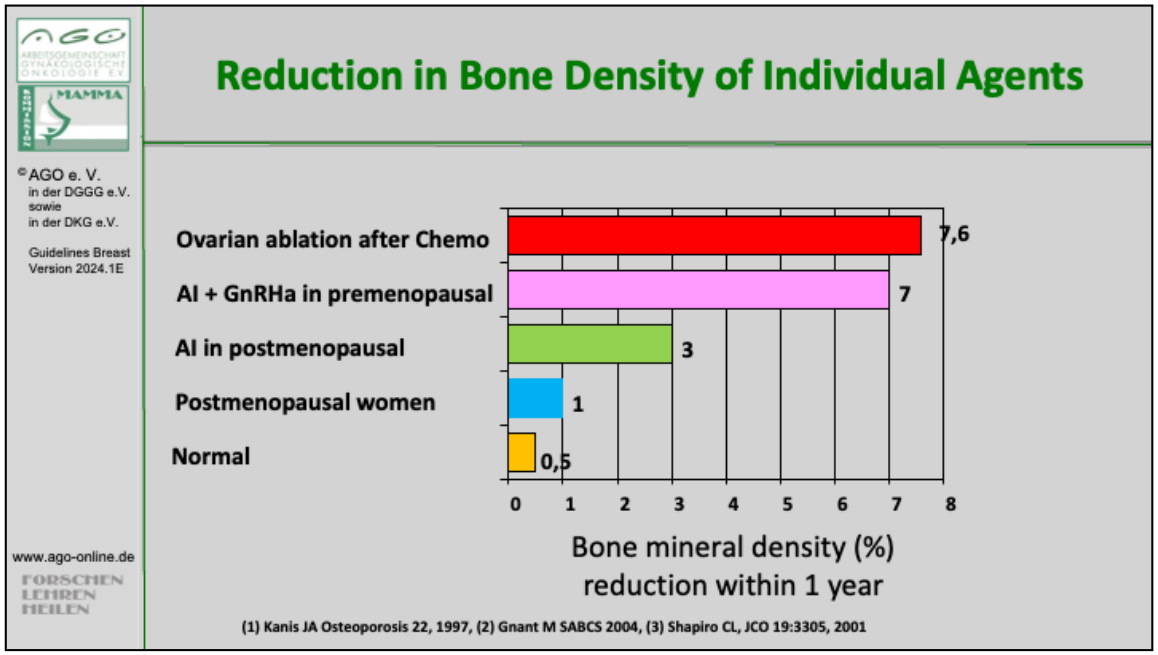
1. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35(18):2062-2081, 2017



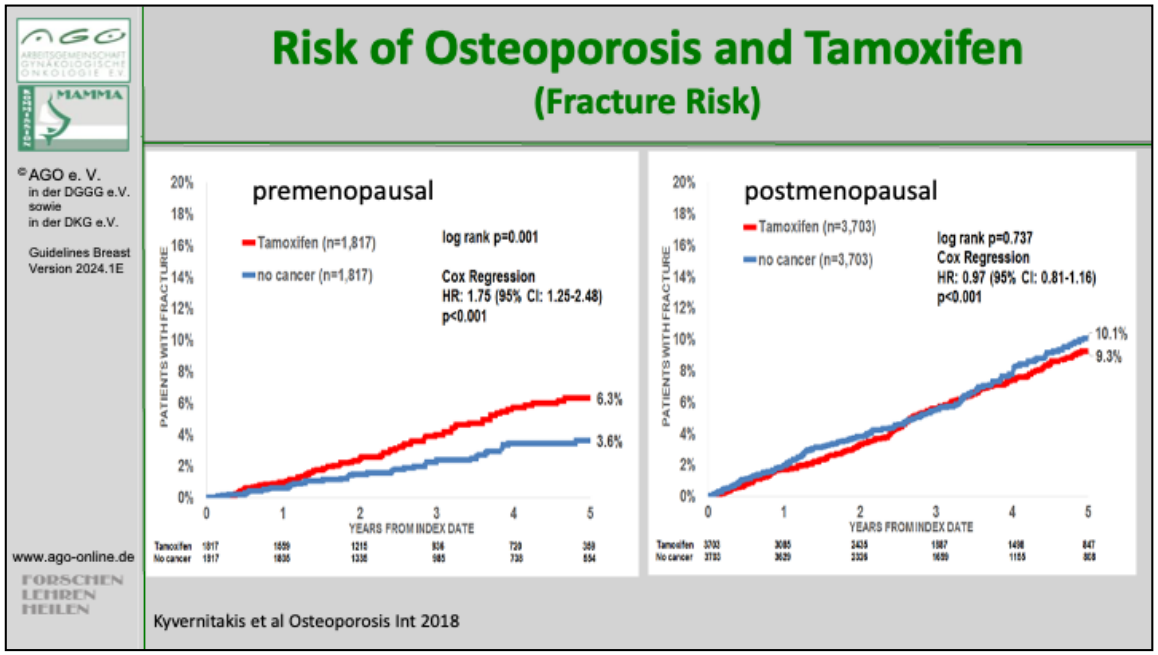
1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 3;386(10001):1353-61, 2015
3. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35(18):2062-2081, 2017
4. Gralow JR, Barlow WE, Paterson AHG et al. Phase III randomized trial of bisphosphonates as adjuvant therapy in breast cancer: S0307. J Natl Cancer Inst. 2019. pii: djz215. doi: 10.1093/jnci/djz215



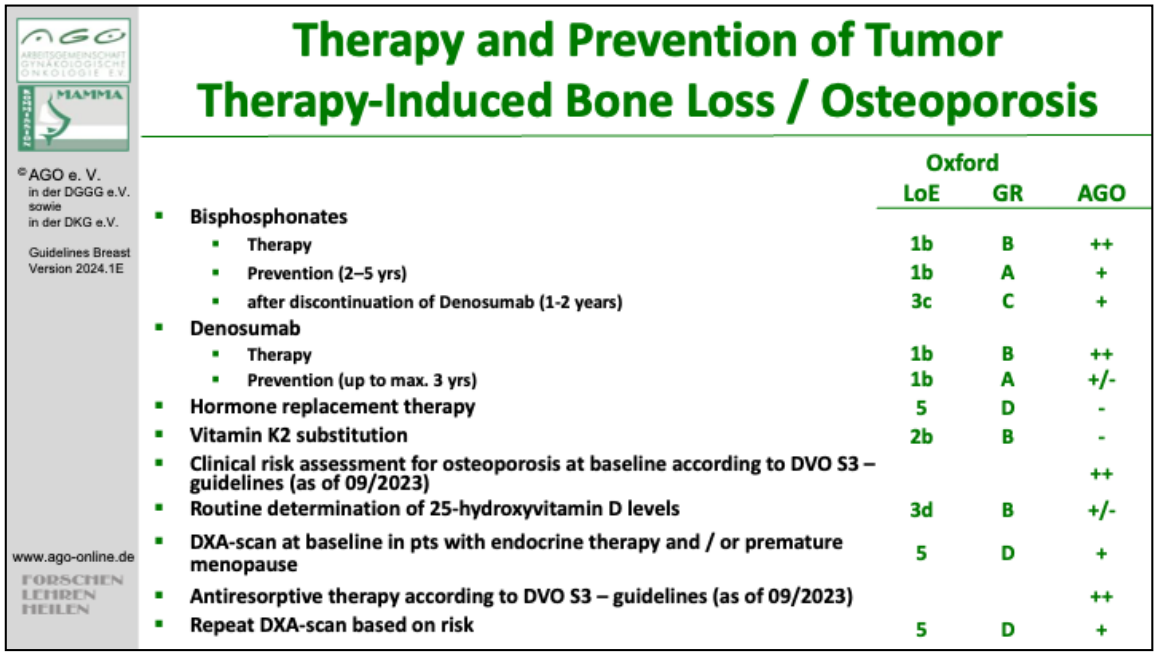
1. Friedl TWP, Fehm T, Müller V, Lichtenegger W, Blohmer J, Lorenz R, Forstbauer H, Fink V, Bekes I, Huober J, Jückstock J, Schneeweiss A, Tesch H, Mahner S, Brucker SY, Heinrich G, Häberle L, Fasching PA, Beckmann MW, Coleman RE, Janni W, Rack B. Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Aug 1;7(8):1149-1157. doi: 10.1001/jamaoncol.2021.1854. PMID: 34165508; PMCID: PMC8227465.



1. Kanis JA, Delmas P, Burckhardt P et al. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int 1997;7(4):390-406. doi: 10.1007/BF01623782.
2. Shapiro CL, Manola J, Leboff MJ. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol. 2001;19(14):3306-11. doi: 10.1200/JCO.2001.19.14.3306.



1. Kyvernitakis I, Kostev K, Hadji P. The tamoxifen paradox-influence of adjuvant tamoxifen on fracture risk in pre- and postmenopausal women with breast cancer. Osteoporos Int. 2018 Nov;29(11):2557-2564.



	Oxford LoE	Oxford 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	+

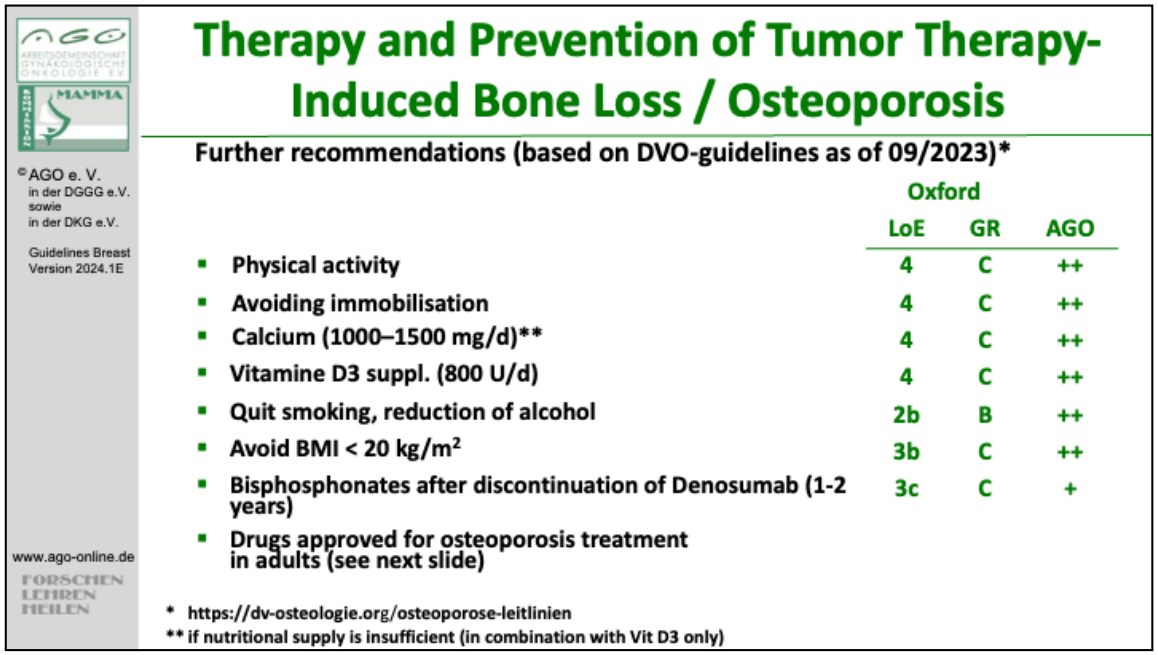
1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
2. Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und Männern ab dem 50.Lebensjahr: Leitlinie des Dachverbandes der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V. 2023; Langfassung V2.1. AWMF-Register-Nr.: 183/001; https://dv-osteologie.org/osteoporose-leitlinien
3. Gnant M, Pfeiler G, Dubsky PC et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 386(9992):433-43, 2015
4. Hadji P, Coleman RE, Wilson C. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol 27(3):379-90, 2016
5. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
6. Chukir T, Liu Y, Farooki A. Antiresorptive agents' bone-protective and adjuvant effects in postmenopausal women with early breast cancer. Br J Clin Pharmacol. 2019 Jun;85(6):1125-1135.
7. Pineda-Moncusí M, Garcia-Giralt N, Diez-Perez A et al. Increased Fracture Risk in Women Treated With Aromatase Inhibitors Versus

Tamoxifen: Beneficial Effect of Bisphosphonates. J Bone Miner Res. 2019 Oct 9. doi: 10.1002/jbmr.3886.

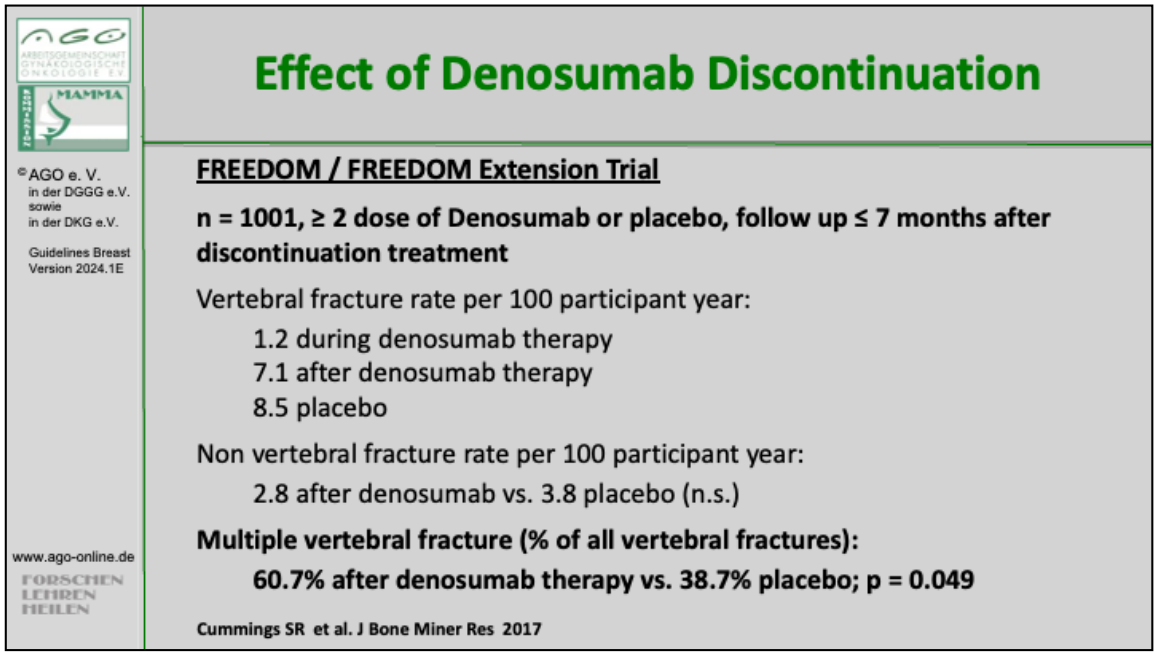
8. Anastasilakis AD, Makras P , Yavropoulou MP. Denosumab Discontinuation and the Rebound Phenomenon: A Narrative Review. J. Clin. Med. 2021, 10, 152. https://doi.org/10.3390/jcm10010152

Vitamin K

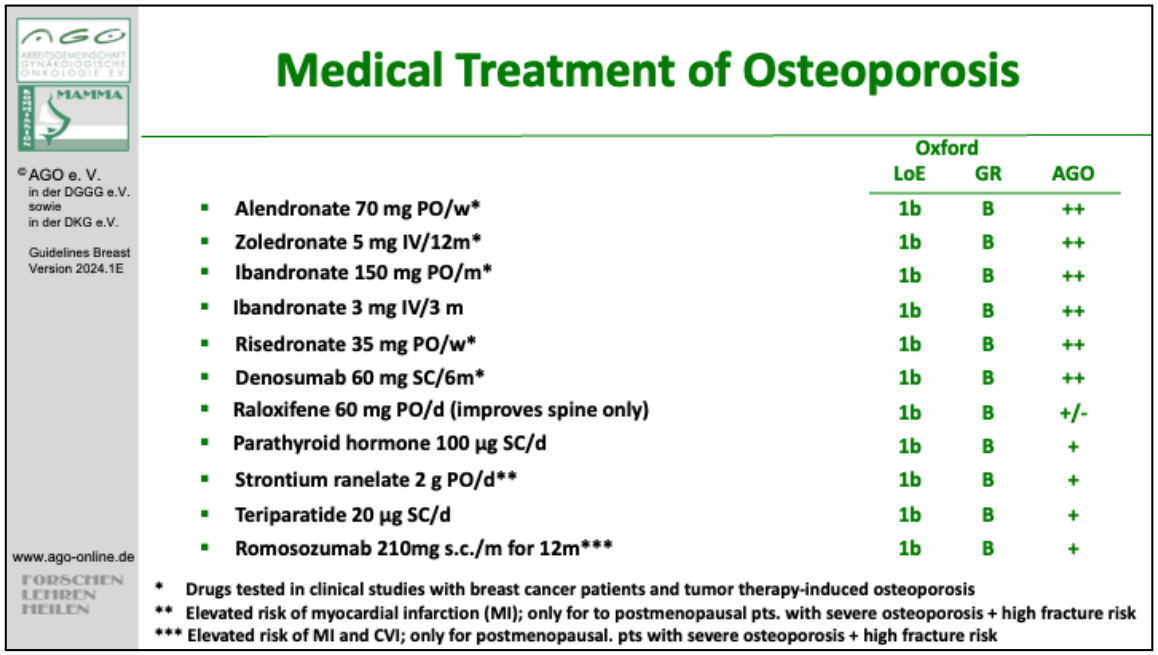
1. Rønn, S. H., Harsløf, T., Pedersen, S. B., & Langdahl, B. L. (2016). Vitamin K2 (menaquinone-7) prevents age-related deterioration of trabecular bone microarchitecture at the tibia in postmenopausal women. European journal of endocrinology, 175(6), 541-549.LoE2
2. Su S, He N, Men P, Song C, Zhai S. The efficacy and safety of menatetrenone in the management of osteoporosis: a systematic review and meta-analysis of randomized controlled trials. Osteoporos Int. 2019 Jun;30(6):1175-1186. doi: 10.1007/s00198-019-04853-7. Epub 2019 Feb 7. Erratum in: Osteoporos Int. 2021 Oct;32(10):2141-2142. PMID: 30734066.



1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019
3. Hadji P, Coleman RE, Wilson C et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol 27(3):379-90, 2016
4. Chapurlat R. Effects and Management of Denosumab Discontinuation. Joint Bone Spine. 2018 Jan 6. pii: S1297-319X(18)30001-0. doi: 10.1016/j.jbspin.2017.12.013
6. Tsourdi E, Langdahl B, Cohen-Solal M et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone 105:11-17, 2017
7. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf
8. German guidelines for the treatment of osteoporosis by the DVO: AWMF-Register-Nr.: 183/001; https://www.dv-osteologie.org/uploads/Leitlinie%202017/Finale%20Version%20Leitlinie%20Osteoporose%202017_end.pdf



1. Cummings SR, Ferrari S, Eastell R et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res. 2018 Feb;33(2):190-198.



1. German guidelines for the treatment of osteoporosis by the DVO: AWMF-Register-Nr.: 183/001; https://www.dv-osteologie.org/uploads/Leitlinie%202017/Finale%20Version%20Leitlinie%20Osteoporose%202017_end.pdf
2. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
3. Hadji P, Coleman RE, Wilson C et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol 2016; 27(3):379-90

Raloxifen

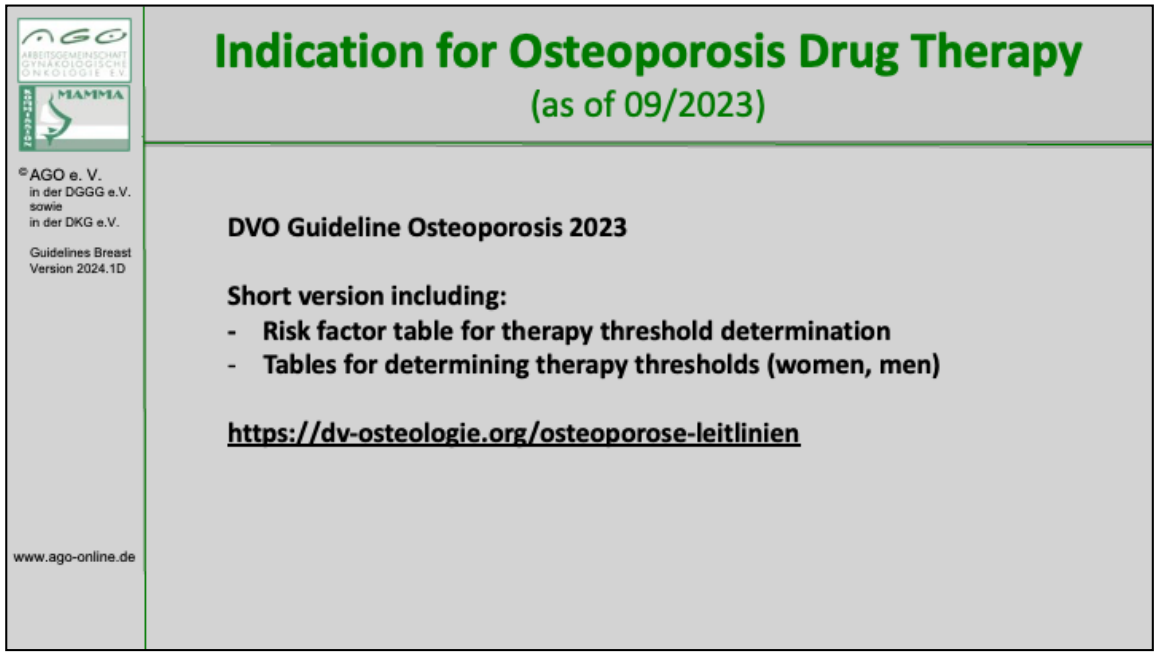
1. Seeman E, Crans GG, Diez-Perez AAnti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int 17(2):313, 2006

Strontium renalate

1. Kaufman JM, Audran M, Bianchi G et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. J Clin Endocrinol Metab 98(2): 592-601, 2013
2. Reginster, J. Y. Cardiac concerns associated with strontium ranelate. Expert Opin Drug Safe 13(9): 1209-1213, 2014

Romosozumab

1. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417-27. https://doi.org/10.1056/nejmoa1708322
2. F. Cosman, D.B. Crittenden, J.D. Adachi, N. Binkley, E. Czerwinski, S. Ferrari, et al., Romosozumab treatment in postmenopausal women with osteoporosis, N. Engl. J. Med. 375 (16) (2016) 1532–1543, https://doi.org/10.1056/NEJMoa1607948
3. Geusens P, Feldman R , Oates M et al Romosozumab reduces incidence of new vertebral fractures across severity grades among postmenopausal women with osteoporosis. Bone 2022 Jan;154:116209. doi: 10.1016/j.bone.2021.116209



1. https://dv-osteologie.org/osteoporose-leitlinien