Guidelines Breast
Version 2024.1D

FORSCHEN
LEHREN
HEILEN

ZNS-Metastasen beim Mammakarzinom

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Version 2024.1D

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- **Versionen 2003-2023:**
  Bauerfeind / Bischoff / Diel / Ditsch / Fehm / Friedrich / Gerber / Huober / Krug / Loibl / Lück / Lüftner / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Park-Simon / Rody / Schütz / Solbach / Stickeler / Witzel

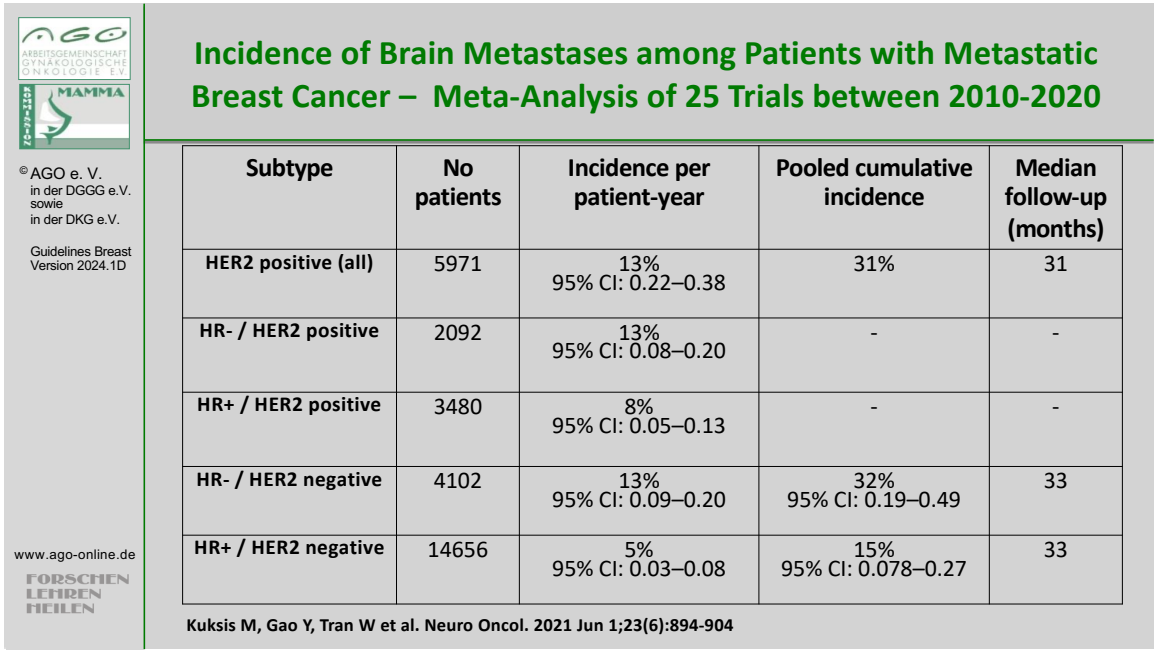
- **Version 2024:**
  Maass / Witzel

ZNS-Metastasen beim Mammakarzinom

- **Das Mammakarzinom ist zweithäufigste Ursache von ZNS-Metastasen.**
- **In Kollektiven von Patientinnen mit metastasiertem Mammakarzinom:**
  - **Parenchymale ZNS-Metastasen: ~ 30–40 %**
  - **Leptomeningeale ZNS-Metastasen: 5–16 %**
- **Steigende Inzidenz (bis zu 40 %)**
- **Anstieg der Inzidenz verursacht durch:**
  - **Effektivere Behandlungsoptionen der extrazerebralen Metastasen**
  - **Vermehrter Einsatz der MR-Diagnostik**
- **Keine Evidenz für Hirnmetastasen-Screening bei asymptomatischen Patientinnen.**
- **Datenlage für Behandlung von ZNS-Metastasen des Mammakarzinoms ist unbefriedigend, da Studien meist nicht Mammakarzinom-spezifisch. Teilnahme an der deutschen Registerstudie zu ZNS-Metastasen Mammakarzinom empfohlen (www.gbg.de).**

1. Duchnowska R, Jassem J, Goswami CP et al.: Predicting early brain metastases based on clinicopathological factors and gene expression analysis in advanced her2-positive breast cancer patients. J Neurooncol 2015;122:205-216.
2. Duchnowska R, Sperinde J, Chenna A et al.: Quantitative her2 and p95her2 levels in primary breast cancers and matched brain metastases. Neuro Oncol 2015;17:1241-1249.
3. Fidler IJ: The biology of brain metastasis: Challenges for therapy. Cancer journal (Sudbury, Mass) 2015;21:284-293
4. Kim, Y.J., J.S. Kim, and I.A. Kim, Molecular subtype predicts incidence and prognosis of brain metastasis from breast cancer in SEER database. J Cancer Res Clin Oncol, 2018. 144(9): p. 1803-1816.
5. Lamba N, Cagney DN, Catalano PJ, et al. Incidence proportion and prognosis of leptomeningeal disease among patients with breast vs. non-breast primaries. Neuro Oncol. 2023 May 4;25(5):973-983.
6. Le Rhun E, Taillibert S, Chamberlain MC: Neoplastic meningitis due to lung, breast, and melanoma metastases. Cancer Control 2017;24:22-32.
7. Mustacchi G, Biganzoli L, Pronzato P et al.: Her2-positive metastatic breast cancer: A changing scenario. Crit Rev Oncol Hematol 2015;95:78-87.
8. Witzel I, Oliveira-Ferrer L, Pantel K et al.: Breast cancer brain metastases: biology and new clinical perspectives. Breast Cancer Research. 2016; 18(1):8.
9. Valiente, M. et al. The evolving landscape of brain metastasis. Trends Cancer 2018; 4, 176–196.

10. Kuksis M, Gao Y, Tran W et al.: The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis Neuro Oncol. 2021 Jun 1;23(6):894-904.



Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
HER2 positive (all)	5971	13% 95% CI: 0.22–0.38	31%	31
HR- / HER2 positive	2092	13% 95% CI: 0.08–0.20	-	-
HR+ / HER2 positive	3480	8% 95% CI: 0.05–0.13	-	-
HR- / HER2 negative	4102	13% 95% CI: 0.09–0.20	32% 95% CI: 0.19–0.49	33
HR+ / HER2 negative	14656	5% 95% CI: 0.03–0.08	15% 95% CI: 0.078–0.27	33

Kuksis M, Gao Y, Tran W et al. Neuro Oncol. 2021 Jun 1;23(6):894-904

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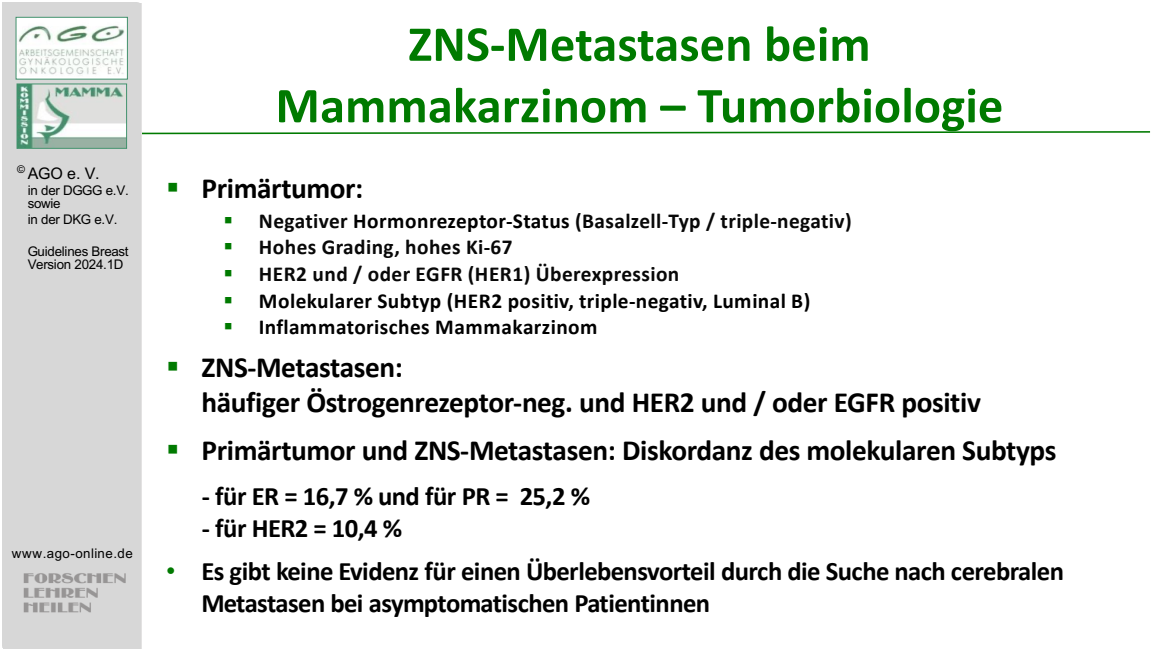


Risk factors (see also references slide CNS incidence)

1. Pivot X, Manikhas A, Zurawski B et al.: Cerebel (egf111438): A phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2015;33:1564-1573.
2. Soni A, Ren Z, Hameed O et al.: Breast cancer subtypes predispose the site of distant metastases. Am J Clin Pathol 2015;143:471-478.
3. Shen Q, Sahin AA, Hess KR et al.: Breast cancer with brain metastases: Clinicopathologic features, survival, and paired biomarker analysis. Oncologist 2015;20:466-473.
4. Warren LEG, Niman SM, Remolano MC et al. Incidence, characteristics, and management of central nervous system metastases in patients with inflammatory breast cancer. Cancer 2022 Dec 1;128(23):4085-4094.

Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR

1. Kuksis M, Gao Y, Tran W et al.: The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis Neuro Oncol. 2021 Jun 1;23(6):894-904.
2. Han CH, Brastianos PK: Genetic characterization of brain metastases in the era of targeted therapy. Frontiers in oncology 2017;7:230.
3. Kaidar-Person O, Meattini I, Jain P et al.: Discrepancies between biomarkers of primary breast cancer and subsequent brain metastases: An international multicenter study. Breast Cancer Res Treat 2018. Jan;167(2):479-483

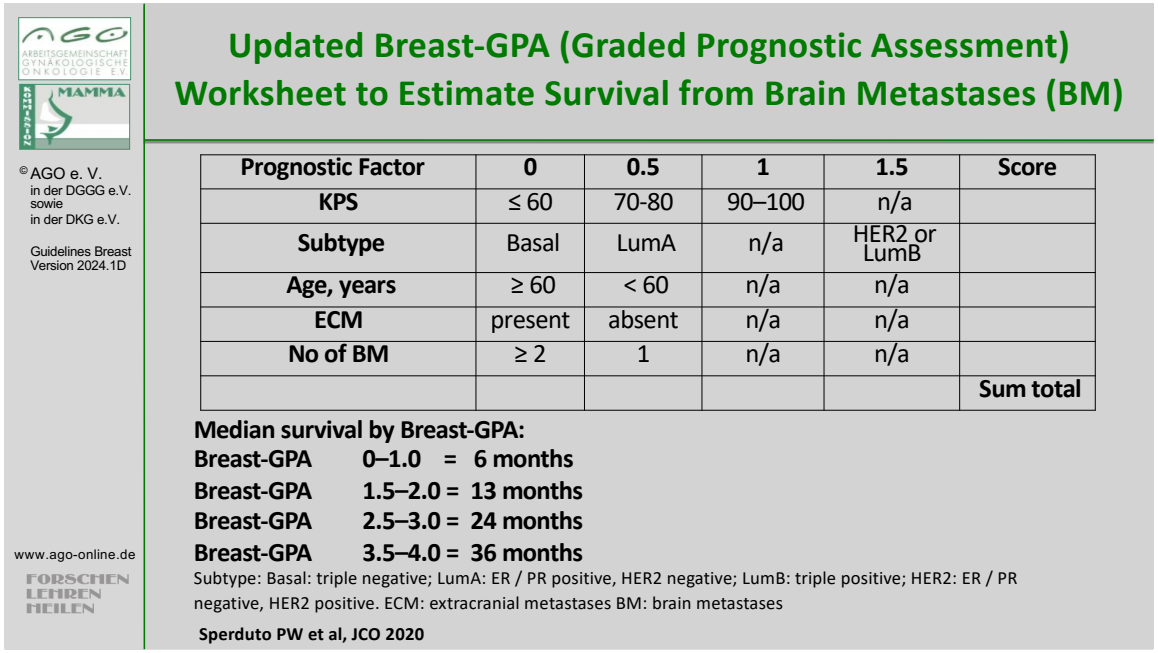
4. Timmer M, Werner JM, Rohn G et al.: Discordance and conversion rates of progesterone-, estrogen-, and her2/neu-receptor status in primary breast cancer and brain metastasis mainly triggered by hormone therapy. Anticancer Res 2017;37:4859-4865.

Molekulare Diskordanz Primärtumor – Metastase:

1. Hulsbergen AFC, Claes A, Kavouridis VK, et al. Subtype switching in breast cancer brain metastases: a multicenter analysis. Neuro Oncol. 2020 Aug 17;22(8):1173-1181.
2. Morgan AJ, Giannoudis A, Palmieri C. The genomic landscape of breast cancer brain metastases: a systematic review. Lancet Oncol. 2021 Jan;22(1):e7-e17.

There is no evidence for BM-screening in asymptomatic BC-patients

1. Niwinska A, Tacikowska M, Murawska M: The effect of early detection of occult brain metastases in HER2-positive breast cancer patients on survival and cause of death. Int J Radiat Oncol Biol Phys 2010, 77:1134-1139.



Updated Breast-GPA (Graded Prognostic Assessment) Worksheet to Estimate Survival from Brain Metastases (BM)

Prognostic Factor	0	0.5	1	1.5	Score
KPS	≤ 60	70-80	90–100	n/a	
Subtype	Basal	LumA	n/a	HER2 or LumB	
Age, years	≥ 60	< 60	n/a	n/a	
ECM	present	absent	n/a	n/a	
No of BM	≥ 2	1	n/a	n/a	
					Sum total

Median survival by Breast-GPA:

Breast-GPA 0–1.0 = 6 months
Breast-GPA 1.5–2.0 = 13 months
Breast-GPA 2.5–3.0 = 24 months
Breast-GPA 3.5–4.0 = 36 months

Subtype: Basal: triple negative; LumA: ER / PR positive, HER2 negative; LumB: triple positive; HER2: ER / PR negative, HER2 positive. ECM: extracranial metastases BM: brain metastases

Sperduto PW et al, JCO 2020

Breast-GPA

1. Riecke K, Müller V, Weide R et al.: Predicting Prognosis of Breast Cancer Patients with Brain Metastases in the BMBC Registry-Comparison of Three Different GPA Prognostic Scores. Cancers (Basel). 2021 Feb 17;13(4):844.
2. Sperduto PW, Kased N, Roberge D et al.: Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012, 30:419-425.
3. Sperduto PW, Mesko S, Li J et al.: Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient. J Clin Oncol. 2020 Nov 10;38(32):3773-3784.
4. Sperduto PW, Mesko S, Li J, et al.: Beyond an updated Graded Prognostic Assessment (Breast GPA): A prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys 2020 107;334-343.

Prognostic Factors for Survival

1. Castaneda CA, Flores R, Rojas KY et al.: Prognostic factors for patients with newly diagnosed brain metastasis from breast cancer. CNS Oncol 2015;4:137-145.
2. Huttenlocher S, Dziggel L, Hornung D et al.: A new prognostic instrument to predict the probability of developing new cerebral metastases after radiosurgery alone. Radiation oncology 2014;9:215.
3. Laakmann, E., K. Riecke, Y. Goy et al.: (2016). "Comparison of nine prognostic scores in patients with brain metastases of breast

cancer receiving radiotherapy of the brain." J Cancer Res Clin Oncol 142(1): 325-332.
4. Nagtegaal SHJ, Claes A, Suijkerbuijk KPM,et al.: Comparing survival predicted by the diagnosis-specific Graded Prognostic Assessment (DS-GPA) to actual survival in patients with 1-10 brain metastases treated with stereotactic radiosurgery. Radiother Oncol. 2019 Sep;138:173-179. doi:.
5. Rades D, Huttenlocher S, Hornung D et al.: Do patients with very few brain metastases from breast cancer benefit from whole-brain radiotherapy in addition to radiosurgery? Radiation oncology 2014;9:267.
6. Subbiah IM, Lei X, Weinberg JS et al.: Validation and development of a modified breast graded prognostic assessment as a tool for survival in patients with breast cancer and brain metastases. J Clin Oncol 2015;33:2239-2245.

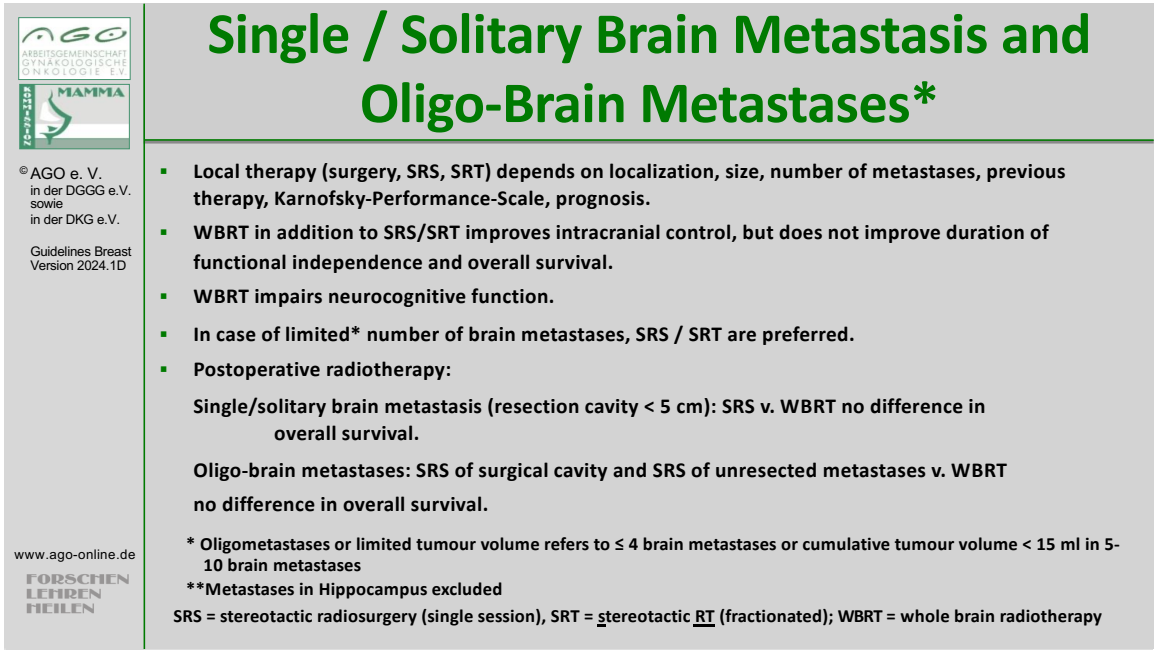
Singuläre Hirnmetastasen und Oligohirnmetastasen*

	Oxford		
	LoE	GR	AGO
Alleinige Lokaltherapie: SRS (< 2-3 cm) oder SRT (>2-4 cm)	1b	B	++
Singuläre Metastase	1b	B	++
OP (wenn indiziert) + Bestrahlung des Tumorbetts (ohne WBRT)			
Oligometastasen	1b	B	++
OP (wenn indiziert) + Bestrahlung des Tumorbetts und SRS oder SRT der nicht-resezierten Metastasen (ohne WBRT)			
WBRT + Boost (SRS, SRT) oder Resektion + WBRT	2a	B	+
Alleinige WBRT	2b	B	+
Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand			
Hippocampusschonung (bei günstiger Prognose)**	1b	B	+

* Oligohirnmetastasierung oder limitierte Metastasierung bezieht sich vor allem auf bis zu 4 Hirnmetastasen, unter bestimmten Voraussetzungen bis zu 10 (Gesamtvolumen < 15 ml)
** Ausschlusskriterium: Metastasen in der Hippocampus-Region
[SRS = stereotactic radiosurgery (einzeitig); SRT = stereotactic radiotherapy (fraktioniert), WBRT = whole brain radiotherapy]

1. Belderbos JSA, De Ruysscher DKM, De Jaeger K et al.: Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021 May;16(5):840-849.
2. Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.
3. Brown, P.D., et al., Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol, 2017. 18(8): p. 1049-1060.
4. Brown PD, Gondi V, Pugh S et al.:Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC00.J Clin Oncol 2020 Apr 1; 38(10): 1019–1029.
5. Cardoso F, Paluch-Shimon S, Senkus Eet al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.
6. Cho E, Rubinstein L, Stevenson P et al.: The use of stereotactic radiosurgery for brain metastases from breast cancer: Who benefits most? Breast Cancer Res Treat 2015;149:743-749.
7. Gondi V, Bauman G, Bradfield L, et al. Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2022 Jul-Aug;12(4):265-282.
8. Halasz, L. M., H. Uno, M. Hughes et al.: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. Cancer 2016 122(13): 2091-2100.

9. Hartgerink D, Bruynzeel A, Eekers D et al. A Dutch phase III randomized multicenter trial: whole brain radiotherapy versus stereotactic radiotherapy for 4-10 brain metastases. Neurooncol Adv. 2021;3(1):vdab021.
10. Kayama T, Sato S, Sakurada K et al: Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. J Clin Oncol. 2018 Jun 20:JCO2018786186. doi: 10.1200/JCO.2018.78.6186.
11. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011, 29:134-141.
12. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
13. Ling DC, Vargo JA, Wegner RE et al.: Postoperative stereotactic radiosurgery to the resection cavity for large brain metastases: Clinical outcomes, predictors of intracranial failure, and implications for optimal patient selection. Neurosurgery 2015;76:150-156; discussion 156-157; quiz 157.
14. Liu Y, Alexander BM, Chen YH et al.: Salvage whole brain radiotherapy or stereotactic radiosurgery after initial stereotactic radiosurgery for 1-4 brain metastases. J Neurooncol 2015;124:429-437.
15. Miller, J. A., R. Kotecha and J. H. Suh: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. Cancer 2016; 122(20): 3243-3244
16. Mix, M., R. Elmarzouky, T. O'Connor et al.: Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy. J Neurosurg 2016; 125(Suppl 1): 26-30
17. Rodríguez de Dios N, Couñago F, Murcia-Mejía M et al.:Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study. J Clin Oncol. 2021 Oct 1;39(28):3118-3127.
18. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.
19. Tham IW, Lim KH, Koh WY et al.: Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. Cochrane Database Syst Rev. 2014 Mar 1;3:CD009454. doi: 10.1002/14651858.CD009454.pub2.



1. Belderbos JSA, De Ruysscher DKM, De Jaeger K et al.: Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021 May;16(5):840-849
2. Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.
3. Brown, P.D., et al., Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol, 2017. 18(8): p. 1049-1060.
4. Brown PD, Gondi V, Pugh S et al.:Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC00.J Clin Oncol 2020 Apr 1; 38(10): 1019–1029.
5. Cardoso F, Paluch-Shimon S, Senkus Eet al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.
6. Ersoy TF, Mokhtari N, Brainman D et al.: Surgical Treatment of Cerebellar Metastases: Survival Benefits, Complications and Timing Issues. Cancers (Basel). 2021 Oct 20;13(21):5263.
7. Gondi V, Bauman G, Bradfield L, et al. Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2022 Jul-Aug;12(4):265-282.
8. Halasz, L. M., H. Uno, M. Hughes et al.: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. Cancer 2016 122(13): 2091-2100.

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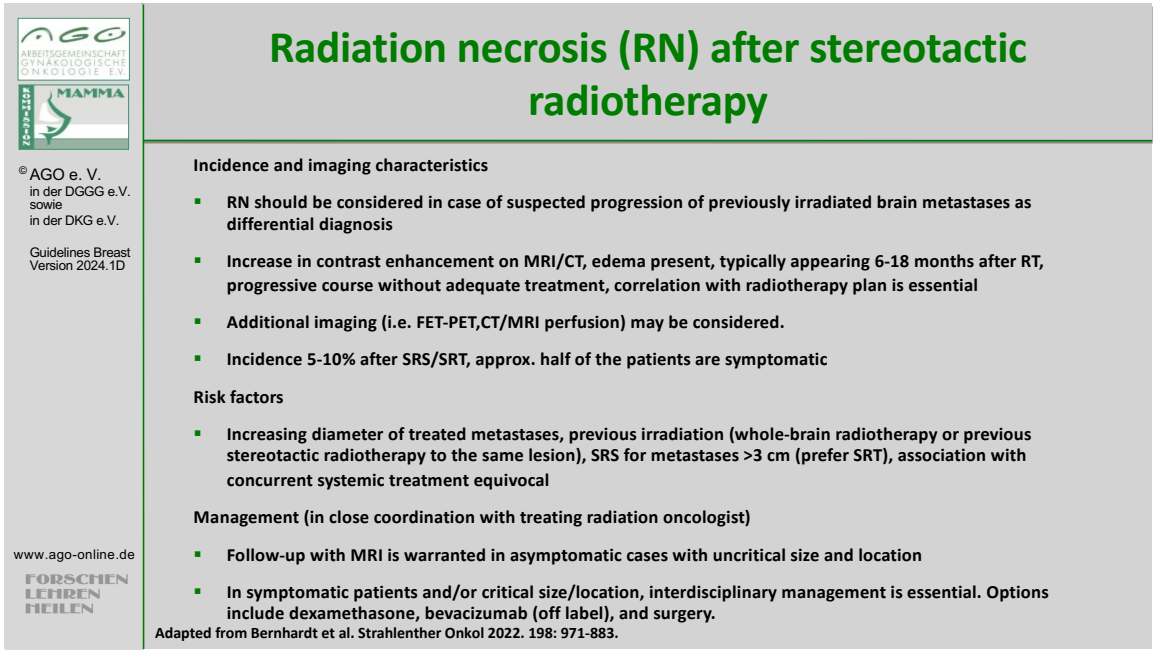
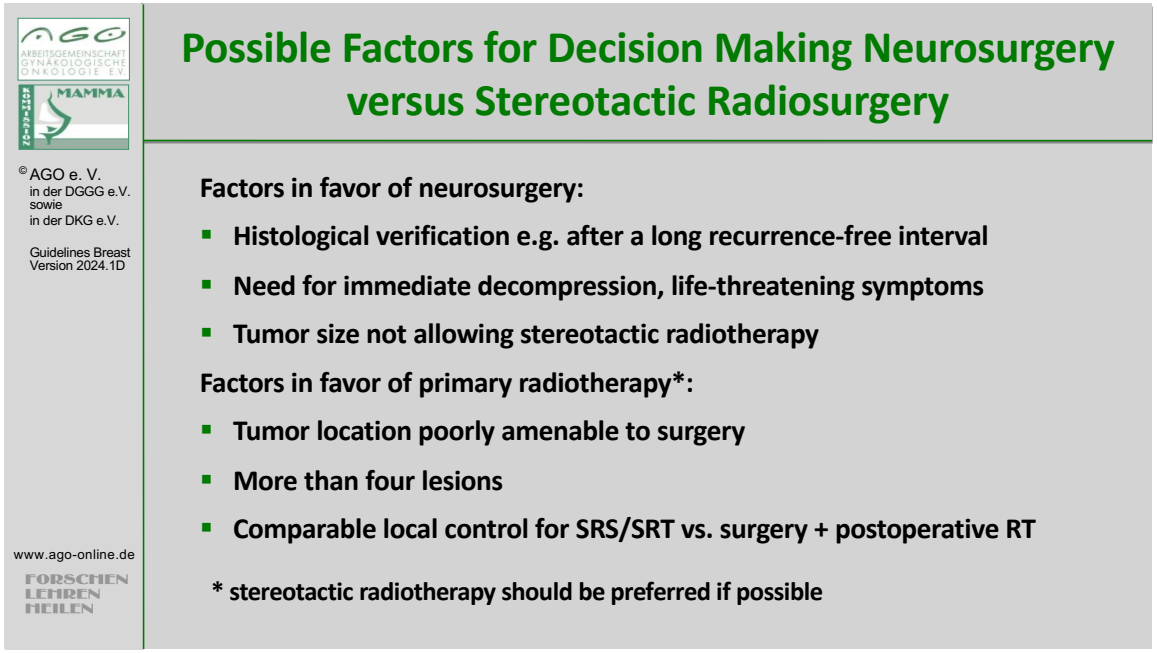
11. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011, 29:134-141.
12. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
13. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.
14. Yamamoto M, Serizawa T, Shuto T et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014;15(4):387-95.



1. Bernhardt D, König L, Grosu A, et al.: Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guideline for central nervous system radiation necrosis part 1: classification and a multistep approach for diagnosis. Strahlenther Onkol. 2022 Oct;198(10):873-883. doi: 10.1007/s00066-022-01994-3. Epub 2022 Aug 29. PMID: 36038669; PMCID: PMC9515024.
2. Bernhardt D, König L, Grosu et al.: Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guideline for central nervous system radiation necrosis part 2: treatment. Strahlenther Onkol. 2022 Nov;198(11):971-980. doi: 10.1007/s00066-022-01973-8. Epub 2022 Aug 29. PMID: 36038670; PMCID: PMC9581806.



1. Cardoso F, Paluch-Shimon S, Senkus Eet al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.
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3. Le Rhun E, Guckenberger M, Smits M et al. EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021 Nov;32(11):1332-1347.
4. Muacevic A, Wowra B, Siefert A et al. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol. 2008 May;87(3):299-307.
5. Rades D, Bohlen G, Pluemer A et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. Cancer. 2007 Jun 15;109(12):2515-21.

Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

	Oxford LoE	GR	AGO
▪ **WBRT (supportiv Steroide[1])**	1a	A	++
▪ **Hippocampusschonung[2] (bei günstiger Prognose)**	1b	B	+
▪ **Glukokortikoide allein[1]**	3a	B	+/-
▪ **Systemtherapie als alleinige Primärbehandlung**	3a	D	+/-
• **bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv)[3]**	2b	C	+
▪ **Radiochemotherapie**	3b	C	-
▪ **Erneute WBRT bei Rezidiv[4]**	4	C	+/-

[1] Symptomadaptiert; [2]Ausschlusskriterium: Metastasen in der Hippocampus-Region; [3]vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen; [4] Falls lokale Therapien (OP, SRS, SRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangen Bestrahlung, Vorbelastung und Lokalisation

SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy (fractionated); WBRT= whole brain radiotherapy

1. Brown PD, Gondi V, Pugh S et al.:Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC00.J Clin Oncol 2020 Apr 1; 38(10): 1019–1029.
2. Belderbos JSA, De Ruysscher DKM, De Jaeger K et al.: Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021 May;16(5):840-849.
3. Geraud, A., H. P. Xu, P. Beuzeboc et al. "Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer." J Neurooncol. 2016
4. Gondi V, Pugh SL, Tome WA et al.: Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (rtog 0933): A phase II multi-institutional trial. J Clin Oncol 2014;32:3810-3816.
5. Krop IE, Lin NU, Blackwell K et al.: Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA.Ann Oncol. 2015; 26(1):113-9. doi: 10.1093/annonc/mdu486.
6. Rodríguez de Dios N, Couñago F, Murcia-Mejía M et al.:Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study. J Clin Oncol. 2021 Oct 1;39(28):3118-3127.
7. Stokes TB, Niranjan A, Kano H et al.: White matter changes in breast cancer brain metastases patients who undergo radiosurgery

alone compared to whole brain radiation therapy plus radiosurgery. J Neurooncol 2015;121:583-590.

Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases

1. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64-71.
2. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022 Mar;33(3):321-329.
3. Freedman RA, Gelman RS, Melisko ME et al: TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). Journal of Clinical Oncology 2017, 35(15_suppl):1005-1005
4. Lin NU, Borges V, Anders C et al., Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial, J Clin Oncol 2020, 38:2610-2619.
5. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2023 Feb 1;9(2):197-205.
6. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2022;:e225610. doi: 10.1001/jamaoncol.2022.5610. Epub ahead of print. PMID: 36454580; PMCID: PMC9716438.
7. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
8. Werter IM, Remmelzwaal S, Burchell GL, et al. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 ;14(22):5612. doi: 10.3390/cancers14225612. PMID: 36428705; PMCID: PMC9688214.

Radiochemotherapy

1. Ammirati M, Cobbs CS, Linskey ME et al.: The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010, 96:85-96.

2. Lassman AB, Abrey LE, Shah GD et al.: Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol 2006, 78:255-260.

Re-Bestrahlung bei Rezidiv

1. Huang, Z., B. Sun, G. Shen et al.: Brain metastasis reirradiation in patients with advanced breast cancer. J Radiat Res 2016. Oct 5. [Epub ahead of print] DOI 10.1093/jrr/rrw087
2. Minniti, G., C. Scaringi, S. Paolin et al.: Repeated stereotactic radiosurgery for patients with progressive brain metastases. J Neurooncol 2016; 126(1): 91-97.
3. Shen, C. J., M. Lim and L. R. Kleinberg (2016). "Controversies in the Therapy of Brain Metastases: Shifting Paradigms in an Era of Effective Systemic Therapy and Longer-Term Survivorship." Curr Treat Options Oncol 2016; 17(9): 46.

Symptomatische Therapie von Hirnmetastasen

	Oxford		
	LoE	GR	AGO
▪ **Antikonvulsiva nur bei Anfallssymtomatik**	3a	C	+
▪ **Glukokortikoide nur, wenn Symptome und / oder Verdrängungseffekt (Dexamethason mit größter Evidenz)**	3a	C	++
▪ **Für Pat. mit schlechter Prognose best supportive care, und / oder palliative Versorgung ohne weitere Therapie als Option**	5	D	+

Anticonvulsants

1. Lobos-Urbina D, Kittsteiner-Manubens L, Pena J: Is primary prevention with antiepileptic drugs effective in brain tumors or brain metastases? Medwave 2017;17:e6871.
2. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.

Steroids

1. Chang SM, Messersmith H, Ahluwalia M, et al: Anticonvulsant prophylaxis and steroid use in adults with metastatic brain tumors: summary of SNO and ASCO endorsement of the Congress of Neurological Surgeons guidelines.Neuro-Oncology 21(4), 424–427, 2019 | doi:10.1093/neuonc/noz034
2. Chen CC, Rennert RC, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of prophylactic anticonvulsants in the treatment of adults with metastatic brain tumors. Neurosurgery. 2019;84(3):E195-E197
3. Nahed BV, Alvarez-Breckenridge C, Brastianos RK et al. . Congress of neurological surgeons systematic review and evidence-based guidelines on the role of surgery in the management of adults with metastatic brain tumors. Neurosurgery. 2019;84(3):E152-E155.
4. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.

Guidelines Breast
Version 2024.1D

Klinische Einordnung von Hirnmetastasen

Stabile Hirnmetastase (Definition: RECIST / RANO): Stabilisierung nach vorangehender Behandlung der Hirnmetastase(n)

Stabile Hirnmetastase (Definition analog DESTINY-Breast03-Studie): stabile Hirnmetastasen 2 Wochen nach Ganzhirnbestrahlung, keine Symptome, keine Medikation mit Kortikosteroiden, Antikonvulsiva

Aktive Hirnmetastase (Definition analog HER2Climb-Studie):

lokal vorbehandelt: progrediente oder neue Hirnmetastase(n), bei denen keine sofortige erneute lokale Behandlung indiziert ist
oder
lokal unbehandelte Hirnmetastase(n), für die keine sofortige lokale Behandlung indiziert ist.

1. Chukwueke UN, Wen PY. Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. CNS Oncol. 2019 Mar 1;8(1):CNS28.
2. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
3. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
4. Hurvitz SA, Hegg R, Chung WP et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023 Jan 14;401(10371):105-117.
5. Hurvitz SA. A Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients (pts) With HER2-Positive (HER2+) Metastatic Breast Cancer (mBC) With Brain Metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. ESMO 2023

Systemische Therapie von Hirnmetastasen: Allgemeine Grundsätze

	Oxford LoE	GR	AGO
▪ **Interdisziplinäre Behandlungsplanung (Tumorboard)**	5	D	++
▪ **Systemtherapie als alleinige Primärbehandlung**	3a	D	+/-
▪ **bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv)***	2b	C	+
▪ **Beibehalten des aktuellen Therapieschemas bei Erstdiagnose zerebraler Metastase und bei extrazerebral stabiler Erkrankungssituation****	2c	C	+

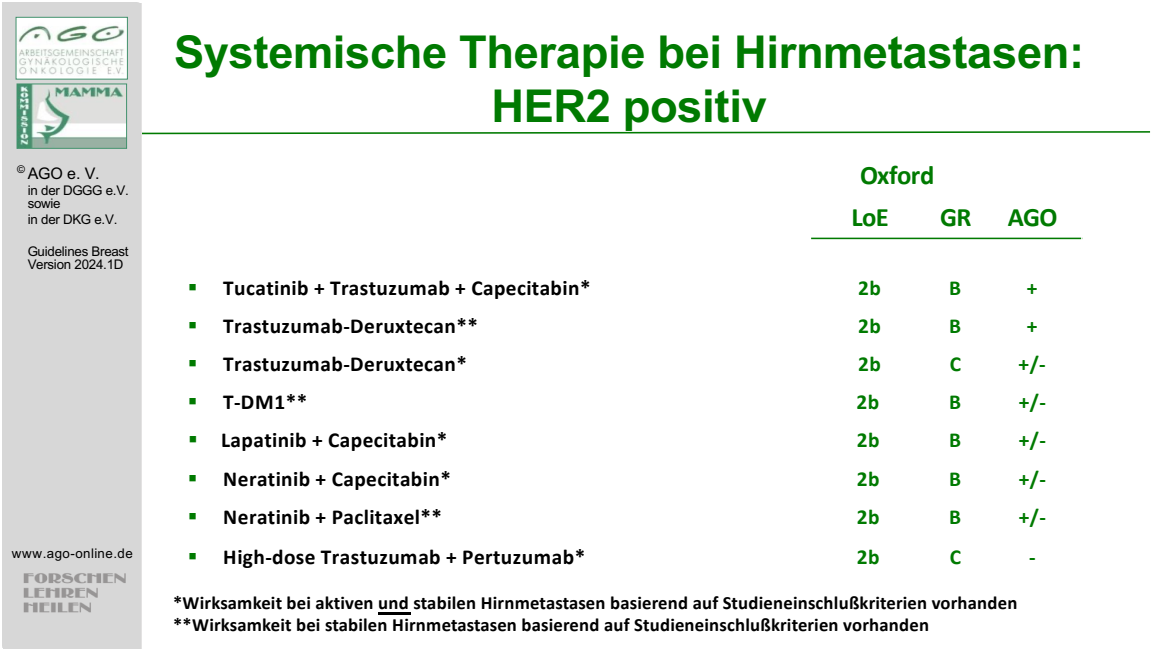
***vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen**
****vorausgesetzt: Adäquate lokale Therapie der Hirnmetastasen**

1. Cardoso F, Paluch-Shimon S, Senkus E et al. . 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649. doi: 10.1016/j.annonc.2020.09.010. Epub 2020 Sep 23. PMID: 32979513; PMCID: PMC7510449.
2. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
3. Ramakrishna N, Anders CK, Lin NU et al. Management of Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases: ASCO Guideline Update. J Clin Oncol. 2022;40(23):2636-2655. doi: 10.1200/JCO.22.00520.
4. Vogelbaum MA, Brown PD, Messersmith H, et al.. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol. 2022 Feb 10;40(5):492-516. doi: 10.1200/JCO.21.02314. Epub 2021 Dec 21. Erratum in: J Clin Oncol. 2022 Apr 20;40(12):1392. PMID: 34932393.

<u>Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases</u>

1. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64-71.
2. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022

Mar;33(3):321-329. doi: 10.1016/j.annonc.2021.12.005. Epub 2021 Dec 23. Erratum in: Ann Oncol. 2022 Dec 21;: PMID: 34954044.
3. Freedman RA, Gelman RS, Anders CK et al: TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. J Clin Oncol. 2019 May 1;37(13):1081-1089
4. Hurvitz SA, Loi S. O`Shaughnessy et al. HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer. SABCS 2023, GS01-10
5. Lin NU, Borges V, Anders C et al., Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial, J Clin Oncol 2020, 38:2610-2619.
6. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2022;:e225610. doi: 10.1001/jamaoncol.2022.5610. Epub ahead of print. PMID: 36454580; PMCID: PMC9716438.
7. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
8. Werter IM, Remmelzwaal S, Burchell GL, et al. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 ;14(22):5612. doi: 10.3390/cancers14225612. PMID: 36428705; PMCID: PMC9688214.



Systemische Therapie bei Hirnmetastasen: HER2 positiv

	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabin*	2b	B	+
▪ Trastuzumab-Deruxtecan**	2b	B	+
▪ Trastuzumab-Deruxtecan*	2b	C	+/-
▪ T-DM1**	2b	B	+/-
▪ Lapatinib + Capecitabin*	2b	B	+/-
▪ Neratinib + Capecitabin*	2b	B	+/-
▪ Neratinib + Paclitaxel**	2b	B	+/-
▪ High-dose Trastuzumab + Pertuzumab*	2b	C	-

*Wirksamkeit bei aktiven und stabilen Hirnmetastasen basierend auf Studieneinschlußkriterien vorhanden
**Wirksamkeit bei stabilen Hirnmetastasen basierend auf Studieneinschlußkriterien vorhanden

Tucatinib + Trastuzumab + Capecitabin:

1. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022 Mar;33(3):321-329.
2. Lin NU, Borges V, Anders C et al., Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial, J Clin Oncol 2020, 38:2610-2619.
3. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2023 Feb 1;9(2):197-205.
4. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
5. Werter IM, Remmelzwaal S, Burchell GL, et al. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 ;14(22):5612.

Trastuzumab-Deruxtecan:

1. Bartsch R, Berghoff AS, Furtner J et al. Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients (pts) with active brain

metastases: Primary outcome analysis from the TUXEDO-1 trial; Ann Oncol 2022;33 (suppl_3): S194-S223. 10.1016/annonc/annonc894
2. Cortés J, Kim SB, Chung WP, Im SA et al; DESTINY-Breast03 Trial Investigators. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022;386(12):1143-1154.
3. Hurvitz SA. A Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients (pts) With HER2-Positive (HER2+) Metastatic Breast Cancer (mBC) With Brain Metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. ESMO 2023
4. Modi S, Saura C, Yamashita T et al., Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer, N Engl J Med. 2020, 382: 610–621.
5. Werter IM, Remmelzwaal S, Burchell GL, de Gruijl TD, Konings IR, van der Vliet HJ, Menke-van der Houven van Oordt CW. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022;14(22):5612. doi: 10.3390/cancers14225612. PMID: 36428705; PMCID: PMC9688214.
6. Yamanaka T, Niikura N, Nomura H et al.: Trastuzumab deruxtecan for the treatment of patients with HER2-positive breast cancer with brain and/or leptomeningeal metastases: A multicenter retrospective study (ROSET-BM study) SABCS 2022;PD7-01

<u>T-DM1:</u>

1. Bartsch R, Berghoff AS, Vogl U et al.: Activity of t-dm1 in her2-positive breast cancer brain metastases. Clin Exp Metastasis 2015;32:729-737
2. Fabi, A., et al., T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer. Breast, 2018. 41: p. 137-143.
3. Jacot, W., E. Pons, J. S. Frenel et al.: Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases." Breast Cancer Res Treat 2016; 157(2): 307-318.
4. Krop IE, Lin NU, Blackwell K et al., Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA, Ann Oncol 2015, 26(1):113-119
5. Hurvitz SA, Loi S. O`Shaughnessy et al. HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer. SABCS 2023, GS01-10
6. Montemurro F, Delaloge S, Barrios CH et al., Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial, Ann Oncol 2020;

31:1350-1358

Lapatinib + Capecitabin:

1. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64-71.

2. Petrelli et al., The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis, Eur J Cancer, 2017;84:141-148

Neratinib + Capecitabin:

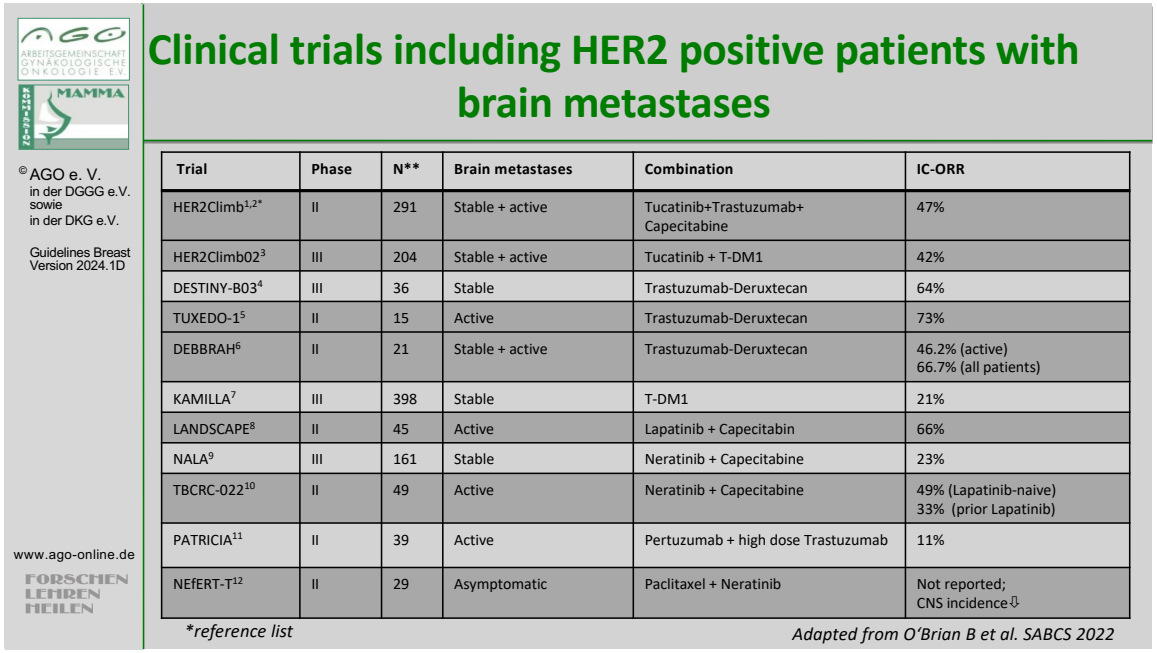
1. Freedman RA, Gelman RS, Melisko ME et al: TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). Journal of Clinical Oncology 2017, 35(15_suppl):1005-1005.
2. Saura C, Oliveira M, Feng YH et al., Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With 2 HER2-Directed Regimens: Phase III NALA Trial, J Clin Oncol. 2020; 38(27):3138-3149

Neratinib + Paclitaxel:

1. Awada A, Colomer R, Inoue K et al., Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial, JAMA Oncol. 2016; 2(12):1557-1564

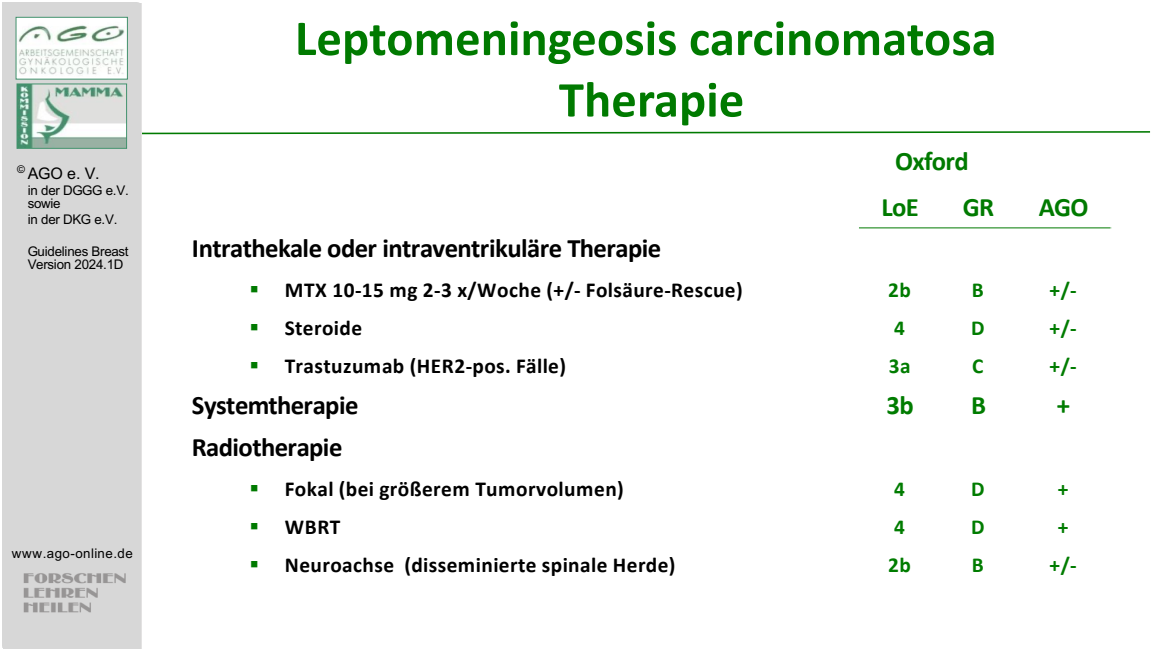
Trastuzumab + Pertuzumab:

1. Lin NU, Pegram M, Sahebjam S, et al. Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study. J Clin Oncol 2021;39(24):2667-2675. doi: 10.1200/JCO.20.02822. Epub 2021 May 4. PMID: 33945296; PMCID: PMC8376355.



1. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2022;:e225610. doi: 10.1001/jamaoncol.2022.5610. Epub ahead of print. PMID: 36454580; PMCID: PMC9716438.
2. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022 Mar;33(3):321-329.
3. Hurvitz SA, Loi S. O`Shaughnessy et al. HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer. SABCS 2023, GS01-10
4. Hurvitz S, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03. Presented at SABCS 2021; December 7-10, 2021; San Antonio, TX. Abstract GS3-01.
5. Bartsch R, Berghoff AS, Furtner J et al. Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients (pts) with active brain metastases: Primary outcome analysis from the TUXEDO-1 trial; Ann Oncol 2022;33 (suppl_3): S194-S223. 10.1016/annonc/annonc894
6. Pérez-García JM, Vaz Batista M, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-

positive breast cancer: The DEBBRAH trial. Neuro Oncol. 2023 Jan 5;25(1):157-166.
7. Montemurro F, Delaloge S, Barrios CH et al., Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial, Ann Oncol 2020; 31:1350-1358
8. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64-71.
9. Saura C, Oliveira M, Feng YH et al., Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With 2 HER2-Directed Regimens: Phase III NALA Trial, J Clin Oncol. 2020; 38(27):3138-3149
10. Freedman RA, Gelman RS, Melisko ME et al: TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). Journal of Clinical Oncology 2017, 35(15_suppl):1005-1005.
11. Lin NU, Pegram M, Sahebjam S, et al. Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study. J Clin Oncol 2021 ;39(24):2667-2675. doi: 10.1200/JCO.20.02822. Epub 2021 May 4. PMID: 33945296; PMCID: PMC8376355.
12. Awada A, Colomer R, Inoue K et al., Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial, JAMA Oncol. 2016; 2(12):1557-1564



Leptomeningeosis carcinomatosa
Therapie

	Oxford		
	LoE	GR	AGO
Intrathekale oder intraventrikuläre Therapie			
▪ **MTX 10-15 mg 2-3 x/Woche (+/- Folsäure-Rescue)**	2b	B	+/-
▪ **Steroide**	4	D	+/-
▪ **Trastuzumab (HER2-pos. Fälle)**	3a	C	+/-
Systemtherapie	3b	B	+
Radiotherapie			
▪ **Fokal (bei größerem Tumorvolumen)**	4	D	+
▪ **WBRT**	4	D	+
▪ **Neuroachse (disseminierte spinale Herde)**	2b	B	+/-

Review:

1. Marowsky M, Müller V, Schmalfeldt B et al. Intrathecal Therapy options for Meningeal Carcinomatosis. Geburtshilfe Frauenheilkd. 2023; 84 (1): 59-67
2. Palmisciano P, Sagoo NS, Kharbat AF, Kenfack YJ, Bin Alamer O, Scalia G, Umana GE, Aoun SG, Haider AS. Leptomeningeal Metastases of the Spine: A Systematic Review. Anticancer Res. 2022;42(2):619-628. doi: 10.21873/anticanres.15519. PMID: 35093859.
3. Razis E, Escudero MJ, Palmieri C et al. Assessment of the management of carcinomatous meningitis from breast cancer globally: a study by the Breast International Group Brain Metastasis Task Force. ESMO Open. 2022

Systemic therapy

1. Le Rhun E, Wallet J, Mailliez A, et al. Intrathecal liposomal cytarabine plus systemic therapy versus systemic chemotherapy alone for newly diagnosed leptomeningeal metastasis from breast cancer. Neuro Oncol. 2020 Apr 15;22(4):524-538.

Methotrexat:

1. Cole BF, Glantz MJ, Jaeckle KA et al.: Quality-of-life-adjusted survival comparison of sustained-release cytosine arabinoside versus intrathecal methotrexate for treatment of solid tumor neoplastic meningitis. Cancer 2003, 97:3053-3060.
2. Glantz MJ, Jaeckle KA, Chamberlain MC et al.: A randomized controlled trial comparing intrathecal sustained-release cytarabine

(DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 1999, 5:3394-3402.
3. Grossman SA, Finkelstein DM, Ruckdeschel JC et al.: Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. J Clin Oncol 1993, 11:561-569.
4. Le Rhun E, Weller M, Brandsma D et al.: Eano-esmo clinical practice guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. Ann Oncol 2017;28:iv84-iv99.

MTX high dose

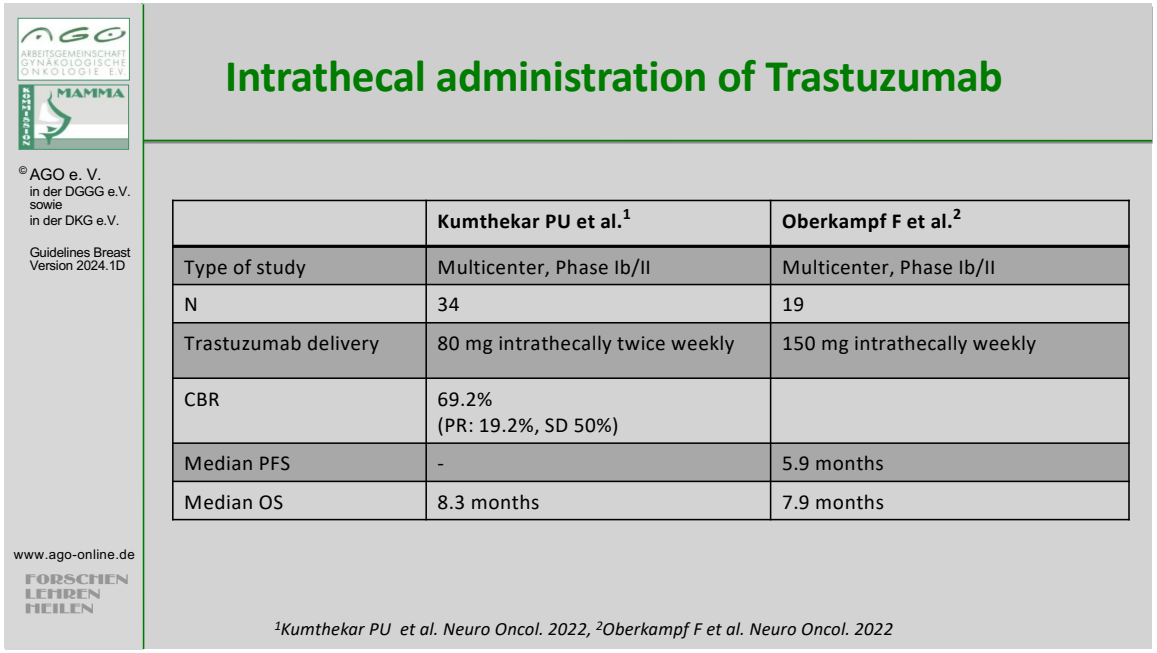
1. Lassman AB, Abrey LE, Shah GD et al.: Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol 2006, 78:255-260.

Trastuzumab intrathecal.

1. Kumthekar PU, Avram MJ, Lassman AB, et al. A Phase I/II Study of Intrathecal Trastuzumab in HER-2 Positive Cancer with Leptomeningeal Metastases: Safety, Efficacy, and Cerebrospinal Fluid Pharmacokinetics. Neuro Oncol. 2022:noac195. doi: 10.1093/neuonc/noac195. Epub ahead of print. PMID: 35948282.
2. Lazaratos AM, Maritan SM, Quaiattini A, et al. Intrathecal trastuzumab versus alternate routes of delivery for HER2-targeted therapies in patients with HER2+ breast cancer leptomeningeal metastases. Breast. 2023 Jun;69:451-468.
3. Oberkampf F, Gutierrez M, Trabelsi Grati O et al. Phase II study of intrathecal administration of trastuzumab in patients with HER2-positive breast cancer with leptomeningeal metastasis. Neuro Oncol. 2022 Jul 22:noac180. doi: 10.1093/neuonc/noac180. Epub ahead of print. PMID: 35868630.
4. Zagouri F, Sergentanis TN, Bartsch R et al.: Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. Breast Cancer Res Treat 2013, 139:13-22

Radiotherapy (Craniospinal irradiation):

1. Wang JT, Wijetunga NA, Pentsova E et al. Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis. J Clin Oncol. 2022;40(33):3858-3867. doi: 10.1200/JCO.22.01148. Epub 2022 Jul 8. PMID: 35802849; PMCID: PMC9671756.



Intrathecal administration of Trastuzumab

	Kumthekar PU et al.[1]	Oberkampf F et al.[2]
Type of study	Multicenter, Phase Ib/II	Multicenter, Phase Ib/II
N	34	19
Trastuzumab delivery	80 mg intrathecally twice weekly	150 mg intrathecally weekly
CBR	69.2% (PR: 19.2%, SD 50%)	
Median PFS	-	5.9 months
Median OS	8.3 months	7.9 months

[1]Kumthekar PU et al. Neuro Oncol. 2022, [2]Oberkampf F et al. Neuro Oncol. 2022

1. Kumthekar PU, Avram MJ, Lassman AB, et al. A Phase I/II Study of Intrathecal Trastuzumab in HER-2 Positive Cancer with Leptomeningeal Metastases: Safety, Efficacy, and Cerebrospinal Fluid Pharmacokinetics. Neuro Oncol. 2022:noac195. doi: 10.1093/neuonc/noac195. Epub ahead of print. PMID: 35948282.
2. Oberkampf F, Gutierrez M, Trabelsi Grati O et al. Phase II study of intrathecal administration of trastuzumab in patients with HER2-positive breast cancer with leptomeningeal metastasis. Neuro Oncol. 2022 Jul 22:noac180. doi: 10.1093/neuonc/noac180. Epub ahead of print. PMID: 35868630.