Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer

- **Versions 2003-2023:**
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- **Version 2024:**
  Maass / Witzel

CNS Metastases in Breast Cancer

- **Breast cancer is the 2nd most common cause of CNS metastases.**
- **In metastatic breast cancer patients:**
  - **Parenchymal CNS metastases: ~ 30–40%**
  - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (up to 40%)**
- **Increasing incidence due to**
  - **More effective treatment of extra-cerebral sites with improved prognosis**
  - **Increasing use of MRI for diagnostic evaluation**
- **Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de).**

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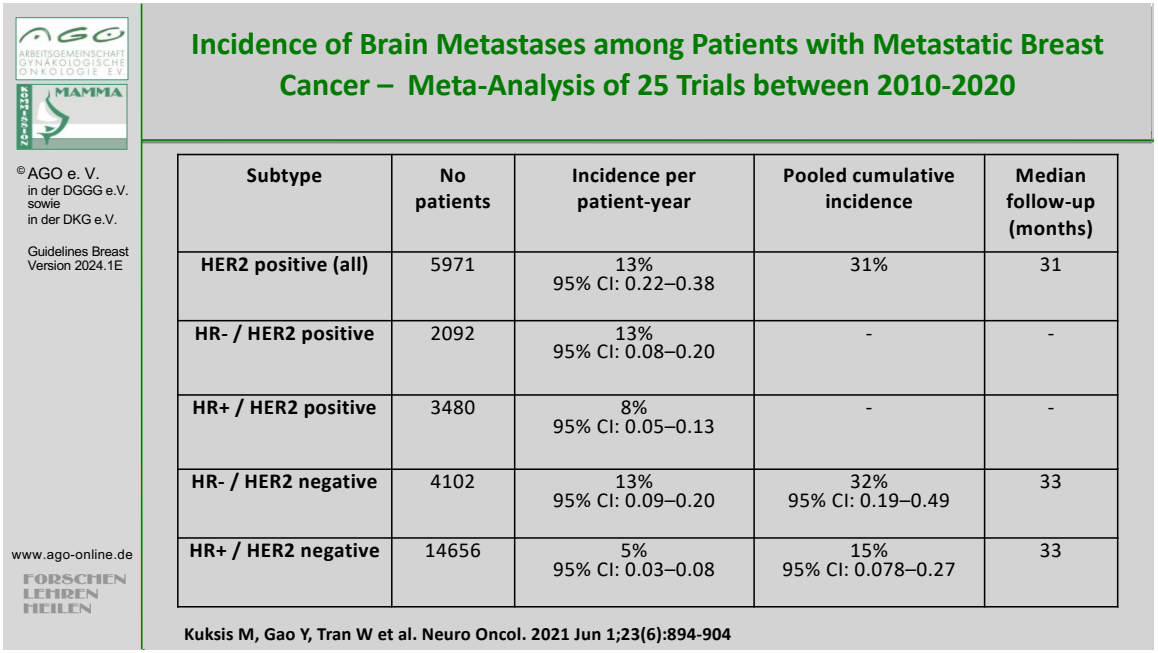

Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

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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CNS Metastases in Breast Cancer
Tumour biology

- **Primary Tumor:**
  - **Negative hormone receptor status (basal-like cell type / triple-negative)**
  - **High grade, high Ki-67 index**
  - **HER2 and / or EGFR (HER1) overexpression**
  - **Molecular subtype (Luminal B, HER2 positive, triple-negative)**
  - **Inflammatory breast cancer**
- **Brain metastases are more likely estrogen receptor negative and overexpress HER2 and / or EGFR.**
- **Discordance of molecular subtype between primary tumor and brain metastases: for ER = 16.7%, for PR = 25.2% and HER2 = 10.4%**
- **There is no evidence for a survival benefit of BM-screening in asymptomatic BC-patients.**

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

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Molekulare Diskordanz Primärtumor – Metastase:

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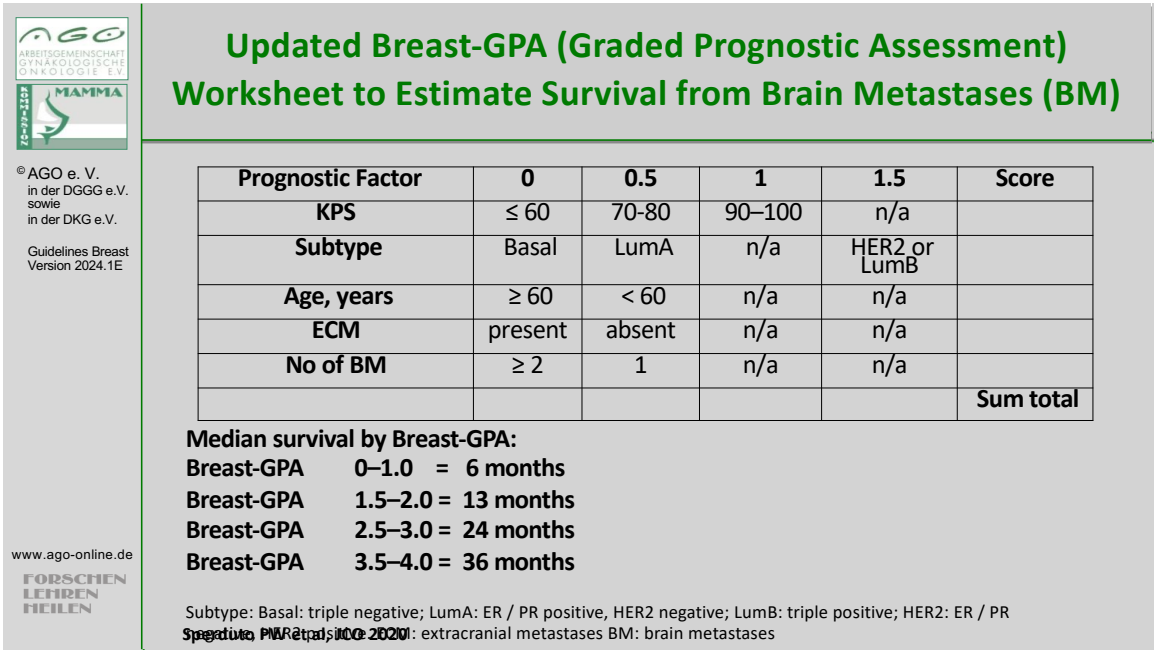
There is no evidence for BM-screening in asymptomatic BC-patients

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)

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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
Sperduto PW et al., IJROBP 2020 negative, HER2 positive ECM: extracranial metastases BM: brain metastases

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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.
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Prognostic Factors for Survival

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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.
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Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (< 2-3 cm) oder SRT (>2-4 cm)	1b	B	++
Single / Solitary Metastasis:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed (without WBRT)			
Oligo-Brain Metastases:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed and SRS or SRT of unresected metastases (without WBRT)			
WBRT + Boost (SRS, SRT) or resection + WBRT	2a	B	+
WBRT alone	2b	B	+
Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing (if prognosis is favourable)**	1b	B	+

* Oligometastases or limited tumour volume refers to ≤ 4 brain metastases or cumulative tumour volume < 15 ml in 5-10 brain metastases

** Metastases in hippocampus excluded

SRS = stereotactic radiosurgery (single session), SRT = stereotactic RT (fractionated); 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.
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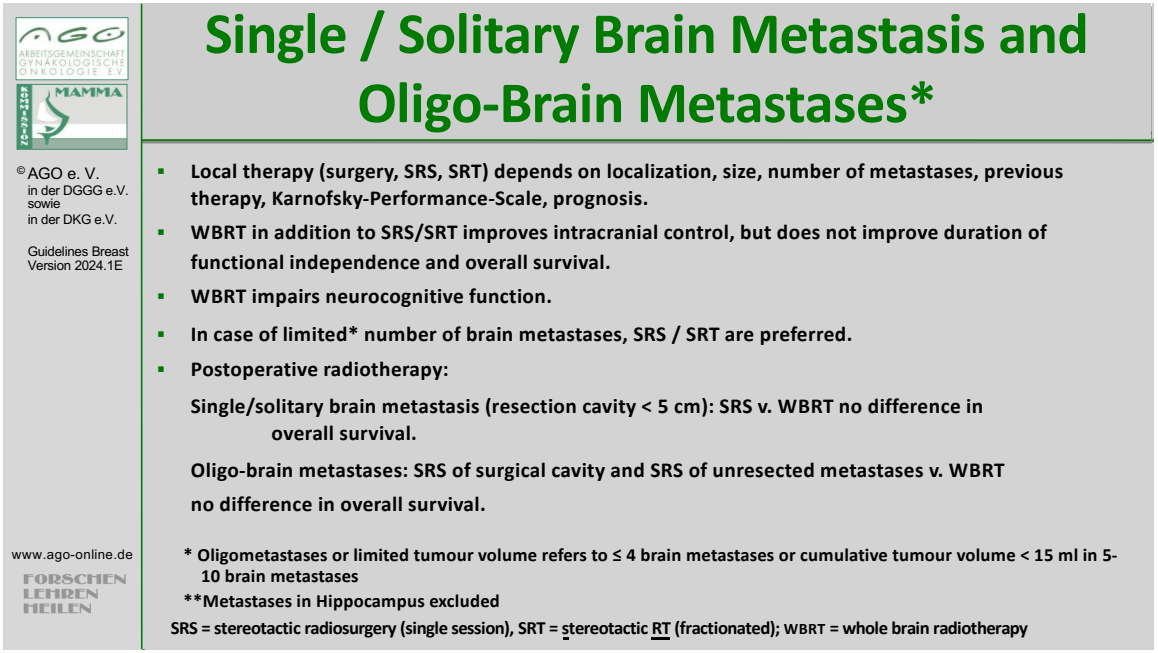

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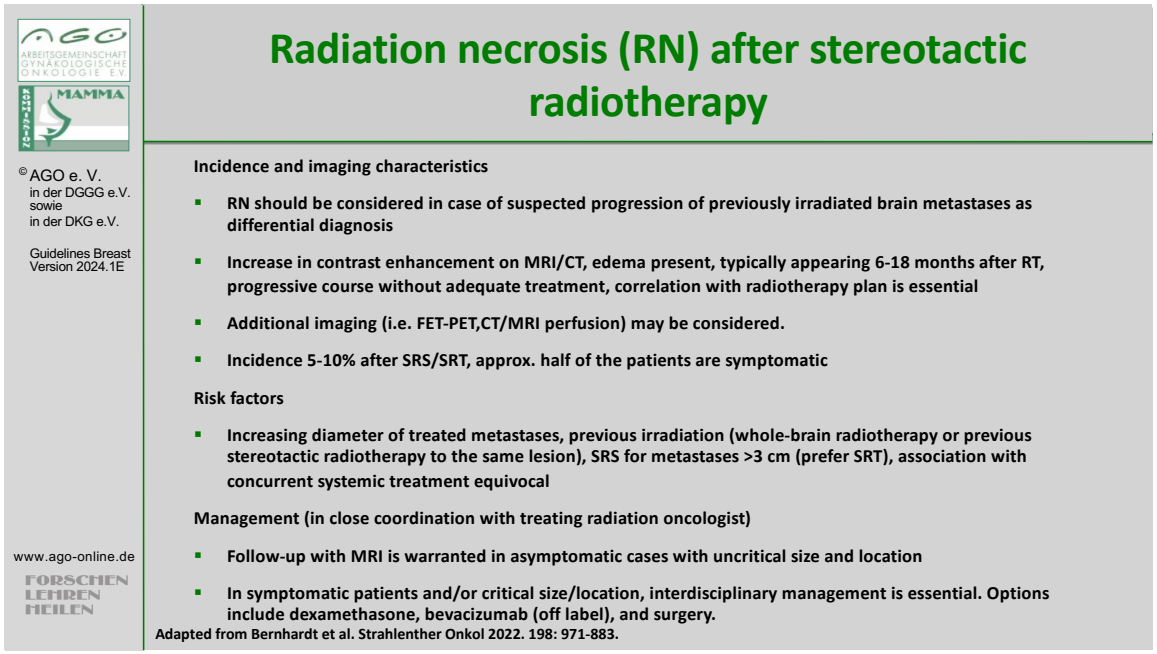

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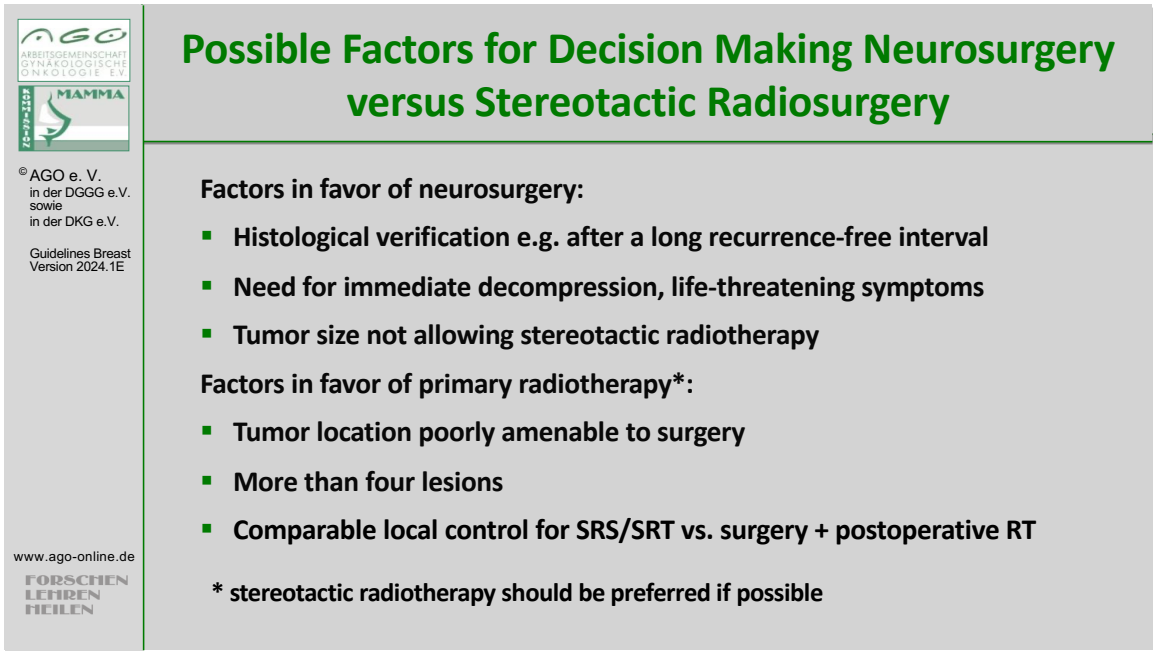

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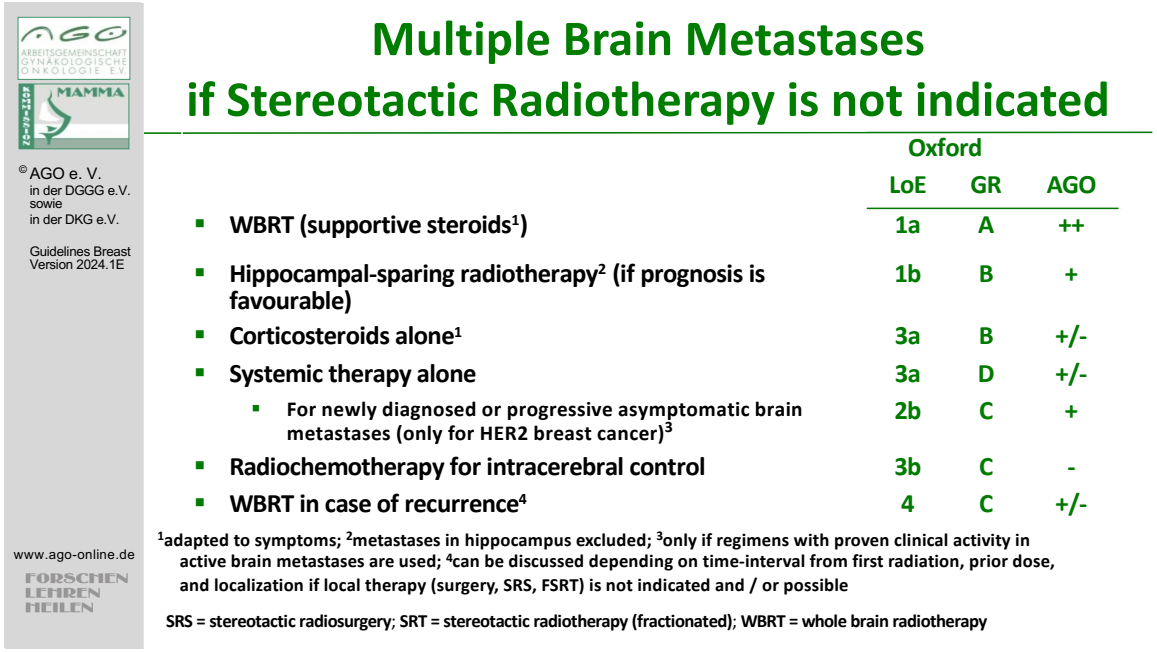

Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated

	Oxford		
	LoE	GR	AGO
▪ WBRT (supportive steroids[1])	1a	A	++
▪ Hippocampal-sparing radiotherapy[2] (if prognosis is favourable)	1b	B	+
▪ Corticosteroids alone[1]	3a	B	+/-
▪ Systemic therapy alone	3a	D	+/-
▪ For newly diagnosed or progressive asymptomatic brain metastases (only for HER2 breast cancer)[3]	2b	C	+
▪ Radiochemotherapy for intracerebral control	3b	C	-
▪ WBRT in case of recurrence[4]	4	C	+/-

[1]adapted to symptoms; [2]metastases in hippocampus excluded; [3]only if regimens with proven clinical activity in active brain metastases are used; [4]can be discussed depending on time-interval from first radiation, prior dose, and localization if local therapy (surgery, SRS, FSRT) is not indicated and / or possible

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.
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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

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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-Radiation recurrence

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.

Guidelines Breast
Version 2024.1E

Symptomatic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Anticonvulsants only if symptoms of seizures	3a	C	+
▪ Glucocorticoids only if symptoms and / or mass effect (Dexamethasone with best evidence)	3a	C	++
▪ For patients with bad prognosis and reduced physical common conditions best supportive care is an 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.

Clinical Classification of Brain Metastases

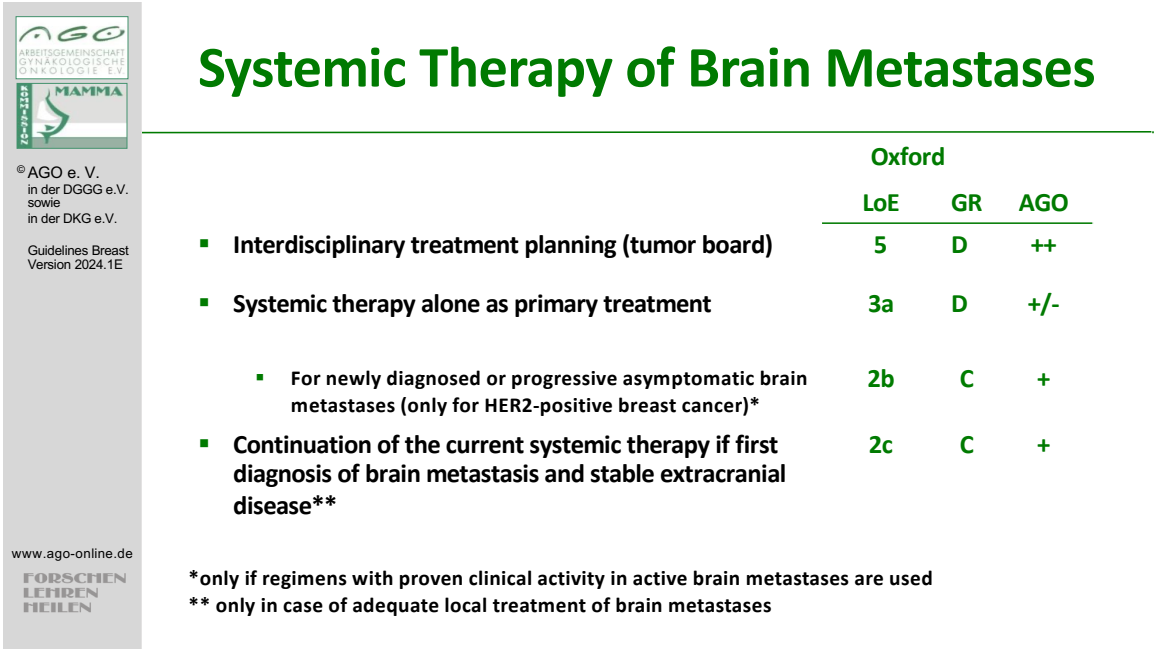
Guidelines Breast
Version 2024.1E

Stable brain metastases (definition: RECIST / RANO):
stabilization after treatment of brain metastases.

Stable brain metastases (definition: DESTINY-BREAST03):
stable brain metastases ≥ 2 weeks after whole brain radiotherapy, asymptomatic, no requirement of corticosteroid or anticonvulsant therapy

Active brain metastases (definition: HER2Climb):
locally pretreated brain metastases with progressive disease or newly diagnosed brain metastases not needing immediate local therapy
or
untreated brain metastases not needing immediate local therapy

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



Systemic Therapy of Brain Metastases

	Oxford LoE	GR	AGO
▪ Interdisciplinary treatment planning (tumor board)	5	D	++
▪ Systemic therapy alone as primary treatment	3a	D	+/-
▪ For newly diagnosed or progressive asymptomatic brain metastases (only for HER2-positive breast cancer)*	2b	C	+
▪ Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease**	2c	C	+

*only if regimens with proven clinical activity in active brain metastases are used
** only in case of adequate local treatment of brain metastases

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.
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Systemic Therapy of Brain Metastases: HER2 positive

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

* efficacy demonstrated in active and stable brain metastases based on trial inclusion criteria
** efficacy demonstrated in stable asymptomatic brain metastases based on trial inclusion criteria

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
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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.
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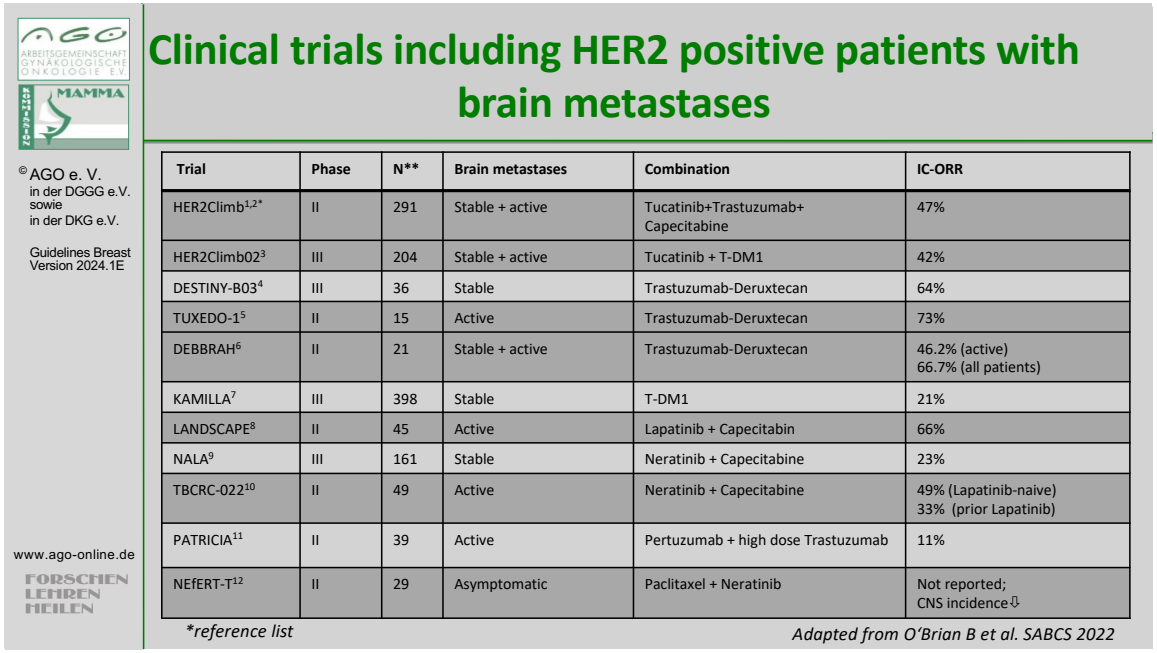
Neratinib + Paclitaxel:

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.



Trial	Phase	N**	Brain metastases	Combination	IC-ORR
HER2Climb[1,2*]	II	291	Stable + active	Tucatinib+Trastuzumab+ Capecitabine	47%
HER2Climb02[3]	III	204	Stable + active	Tucatinib + T-DM1	42%
DESTINY-B03[4]	III	36	Stable	Trastuzumab-Deruxtecan	64%
TUXEDO-1[5]	II	15	Active	Trastuzumab-Deruxtecan	73%
DEBBRAH[6]	II	21	Stable + active	Trastuzumab-Deruxtecan	46.2% (active) 66.7% (all patients)
KAMILLA[7]	III	398	Stable	T-DM1	21%
LANDSCAPE[8]	II	45	Active	Lapatinib + Capecitabin	66%
NALA[9]	III	161	Stable	Neratinib + Capecitabine	23%
TBCRC-022[10]	II	49	Active	Neratinib + Capecitabine	49% (Lapatinib-naive) 33% (prior Lapatinib)
PATRICIA[11]	II	39	Active	Pertuzumab + high dose Trastuzumab	11%
NEfERT-T[12]	II	29	Asymptomatic	Paclitaxel + Neratinib	Not reported; CNS incidence⇩

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
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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

Leptomeningeal Carcinomatosis: Therapy

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
Intrathecal or ventricular therapy			
▪ MTX 10–15 mg 2–3 x/ week (+/- folinic acid rescue)	2b	B	+/-
▪ Steroids	4	D	+/-
▪ Trastuzumab (HER2 pos. disease)	3a	C	+/-
Systemic therapy	3b	B	+
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis Craniospinal irradiation (disseminated spinal lesions)	2b	B	+/-

Review:

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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

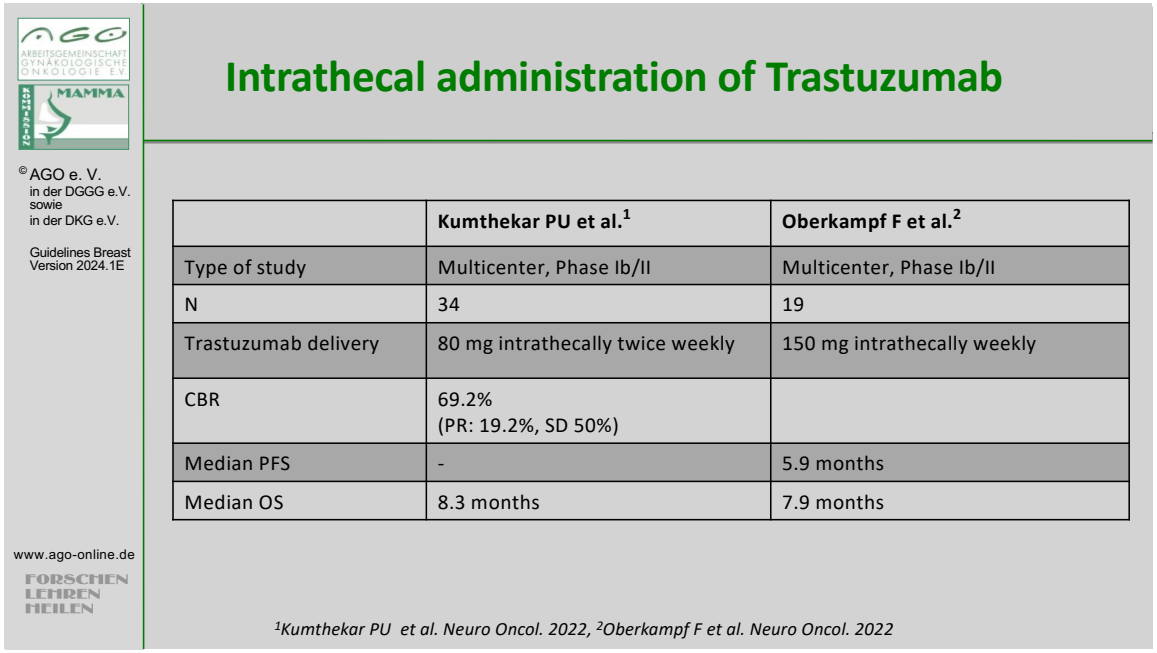
1. Lassman AB, Abrey LE, Shah GD et al.: Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol 2006, 78:255-260.

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):

W ang 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.