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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

CNS Metastases in Breast Cancer



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- **Version 2025:**
Budach / Würstlein

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%); optional biopsy**
- **Increasing incidence due to**
 - **More effective treatment of extra-cerebral sites with improved prognosis**
 - **Increasing use of MRI for diagnostic evaluation**
- **No evidence for screening in asymptomatic patients (trials ongoing).**
- **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).**

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.
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14. Borm K et al :DEGRO guideline for personalized radiotherapy of brain metastases and leptomeningeal carcinomatosis in patients with breast cancer. *Strahlenther Onkol.* 2024 Mar 15;200(4):259–275



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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

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

CNS Metastases in Breast Cancer Tumour biology and Risk Factors

- **Primary Tumor / risk factors:**
 - 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
 - gBRCA mutation
 - Age < 40
 - Lung metastasis
 - Ethnicity
- CNS 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)

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5. Karthik J et al: Navigating breast cancer brain metastasis: Risk factors, prognostic indicators, and treatment perspectives. World J Clin Oncol 2024 May 24; 15(5): 594-598

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

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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; KPS: Karnofsky Performance Status
Sperduto PW et al, JCO 2020

Breast-GPA

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Prognostic Factors for Survival

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cancer receiving radiotherapy of the brain." J Cancer Res Clin Oncol 142(1): 325-332.

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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**	1b	B	+

* Oligometastases refers to ≤ 4 brain metastases


** Metastases in hippocampus excluded

SRS = stereotactic radiosurgery (single session), SRT = stereotactic RT (fractionated); WBRT = whole brain radiotherapy

1. Belderbos JSA, De Ruyscher 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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with breast cancer. *Strahlenther Onkol.* 2024 Mar 15;200(4):259–275.



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Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

* 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

- Local therapy (surgery, SRS, SRT) depends on localization, size, number of metastases, previous therapy, Karnofsky-Performance-Scale, prognosis.
- WBRT in addition to SRS/SRT improves intracranial control, but does not improve duration of functional independence and overall survival.
- WBRT impairs neurocognitive function.
- In case of limited* number of brain metastases, SRS / SRT are preferred.
- Postoperative radiotherapy:
 - Single/solitary brain metastasis (resection cavity < 5 cm): SRS v. WBRT no difference in overall survival.
 - Oligo-brain metastases: SRS of surgical cavity and SRS of unresected metastases v. WBRT no difference in overall survival.

1. Belderbos JSA, De Ruyscher 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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Radiation necrosis (RN) after stereotactic radiotherapy

Incidence and imaging characteristics

- RN should be considered in case of suspected progression of previously irradiated brain metastases as differential diagnosis
- Increase in contrast enhancement on MRI/CT, edema present, typically appearing 6-18 months after RT, progressive course without adequate treatment, correlation with radiotherapy plan is essential
- Additional imaging (i.e. FET-PET,CT/MRI perfusion) may be considered.
- Incidence 5-10% after SRS/SRT, approx. half of the patients are symptomatic

Risk factors

- Increasing diameter of treated metastases, previous irradiation (whole-brain radiotherapy or previous stereotactic radiotherapy to the same lesion), SRS for metastases > 3 cm (prefer SRT), association with concurrent systemic treatment equivocal

Management (in close coordination with treating radiation oncologist, neuro-radiology, and neurosurgery)

- Follow-up with MRI is warranted in asymptomatic cases with uncritical size and location
- In symptomatic patients and/or critical size/location, interdisciplinary management is essential. Options include dexamethasone, bevacizumab (off label), and surgery.

Adapted from Bernhardt et al. Strahlenther Onkol 2022. 198: 971-883.

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Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

Factors in favor of neurosurgery:

- Histological verification e.g. after a long recurrence-free interval
- Need for immediate decompression, life-threatening symptoms
- Tumor size not allowing stereotactic radiotherapy

Factors in favor of primary radiotherapy*:

- Tumor location poorly amenable to surgery
- More than four lesions
- Comparable local control for SRS/SRT vs. surgery + postoperative RT

* stereotactic radiotherapy should be preferred if possible

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Management 5 to 10 Brainmetastasis

	Oxford		
	LoE	GR	AGO
▪ WBRT	1a	A	++
▪ Hippocampal-sparing radiotherapy² (if prognosis is favourable)	1b	B	+
▪ SRS or SRT if volume < 15 ml (without WBRT)	2b	B	+
▪ surgery + radiotherapy and SRS or SRT of non resectable mets (without WBRT)	3a	C	+
▪ Corticosteroids alone¹	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	-

¹adapted to symptoms; ²metastases in hippocampus excluded; ³only if regimens with proven clinical activity in active brain metastases are used;

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

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

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8. Werter IM, Rimmelzwaal 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

Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated

	Oxford		
	LoE	GR	AGO
▪ WBRT	1a	A	++
▪ Hippocampal-sparing radiotherapy² (if prognosis is favourable)	1b	B	+
▪ Corticosteroids alone¹	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 recurrence⁴	4	C	+/-

¹adapted to symptoms; ²metastases in hippocampus excluded; ³only 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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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-GOEC-SEOR Study. J Clin Oncol. 2021 Oct 1;39(28):3118-3127.
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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.

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. Soffiatti 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. Soffiatti 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

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

- 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.
- 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.
- 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.
- 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.
- Borm K et al :DEGRO guideline for personalized radiotherapy of brain metastases and leptomeningeal carcinomatosis in patients with breast cancer. Strahlenther Onkol. 2024 Mar 15;200(4):259–275

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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.
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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, Rimmelzwaal 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.

Systemic Therapy of Brain Metastases: HER2 positive

	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabine*	1b	B	+
▪ Trastuzumab-Deruxtecan*¹	1b	B	+
▪ T-DM1**¹	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
¹ elevated risk for radionecrosis in combination stereotactic radiotherapy and

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.
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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, Rimmelzwaal 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.
6. Yu J et al. Tyrosine kinase inhibitors in HER2-positive breast cancer brain metastases: A systematic review and meta-analysis. Cancer Medicine. 2023;12:15090–15100.

Trastuzumab-Deruxtecan:

1. Bartsch R, Berghoff AS, Furtner J et al. Final outcome analysis from the phase II TUXEDO-1 trial of Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients (pts) with active brain metastases: *Neur Oncol*. 2024 Dec 5; 26 (12) 2305-2315
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.
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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, Rimmelzwaal 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
7. Michelon I et al: Trastuzumab deruxtecan in human epidermal growth factor receptor 2-positive breast cancer brain metastases: a systematic review and meta-analysis. *ESMO open*, 2024, doi.org/10.1016/j.esmoop.2024.102233
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T-DM1:

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.

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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
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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.

Interaction radiosurgery/stereotactic radiotherapy combined with ADCs

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Leptomeningeal Carcinomatosis: Therapy

	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 (as for brain metastases)	2b	B	+
Best supportive care			
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis Craniospinal irradiation (disseminated spinal lesions)	2b	B	+/-

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