CNS Metastases in Breast Cancer
CNS Metastases in Breast Cancer

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

- **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).

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

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

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

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)

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

Molekulare Diskordanz Primärtumor – Metastase:


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

Breast-GPA

Prognostic Factors for Survival


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

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

* 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

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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)
- 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.

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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

Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT (supportive steroids&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Hippocampal-sparing radiotherapy&lt;sup&gt;2&lt;/sup&gt; (if prognosis is favourable)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Corticosteroids alone&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Systemic therapy alone</td>
<td>3a</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>- For newly diagnosed or progressive asymptomatic brain metastases (only for HER2 breast cancer)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Radiotherapy for intracerebral control</td>
<td>3b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>WBRT in case of recurrence&lt;sup&gt;4&lt;/sup&gt;</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<sup>1</sup>adapted to symptoms; <sup>2</sup>metastases in hippocampus excluded; <sup>3</sup>only if regimens with proven clinical activity in active brain metastases are used; <sup>4</sup>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

7. Stokes TB, Niranjan A, Kano H et al.: White matter changes in breast cancer brain metastases patients who undergo radiosurgery

Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases
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 Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2023 Feb 1;9(2):197-205.

Radiochemotherapy

Re-Radiation recurrence

Symptomatic Therapy of Brain Metastases

- **Anticonvulsants only if symptoms of seizures**
  - LoE 3a, GR C, AGO +

- **Glucocorticoids only if symptoms and / or mass effect (Dexamethasone with best evidence)**
  - LoE 3a, GR C, AGO ++

- **For patients with bad prognosis and reduced physical common conditions best supportive care is an option**
  - LoE 5, GR D, AGO +

**Anticonvulsants**

**Steroids**
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

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 (BM) from DESTINY-Breast (DB) -01, -02, and -03. ESMO 2023
Systemic Therapy of Brain Metastases

- Interdisciplinary treatment planning (tumor board)  
  - Oxford LoE GR AGO
  - 5 D ++

- Systemic therapy alone as primary treatment  
  - 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


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


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


**Systemic Therapy of Brain Metastases:**

**HER2 positive**

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucatinib + Trastuzumab + Capecitabine*</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab-Deruxtecan**</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab-Deruxtecan*</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>T-DM1**</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Lapatinib + Capecitabine*</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Neratinib + Capecitabine*</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Neratinib + Paclitaxel**</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>High-dose Trastuzumab + Pertuzumab*</td>
<td>2b</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

* 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 + Capecitabine:**
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.

**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
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
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

T-DM1:
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
Lapatinib + Capecitabin:
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:

Neratinib + Paclitaxel:

Trastuzumab + Pertuzumab:
Clinical trials including HER2 positive patients with brain metastases

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N**</th>
<th>Brain metastases</th>
<th>Combination</th>
<th>IC-ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2CLIMB02</td>
<td>II</td>
<td>291</td>
<td>Stable + active</td>
<td>Tucatinib + Trastuzumab + Capecitabine</td>
<td>47%</td>
</tr>
<tr>
<td>HER2CLIMB02</td>
<td>III</td>
<td>204</td>
<td>Stable + active</td>
<td>Tucatinib + T-DM1</td>
<td>42%</td>
</tr>
<tr>
<td>DESTINY-B03</td>
<td>III</td>
<td>36</td>
<td>Stable</td>
<td>Trastuzumab-Deruxtecan</td>
<td>64%</td>
</tr>
<tr>
<td>TUXEDO-1</td>
<td>II</td>
<td>15</td>
<td>Active</td>
<td>Trastuzumab-Deruxtecan</td>
<td>73%</td>
</tr>
<tr>
<td>DEBBRAH</td>
<td>II</td>
<td>21</td>
<td>Stable + active</td>
<td>Tucatinib-Deruxtecan</td>
<td>46.2% (active) 66.7% (all patients)</td>
</tr>
<tr>
<td>KAMILLA</td>
<td>III</td>
<td>398</td>
<td>Stable</td>
<td>T-DM1</td>
<td>21%</td>
</tr>
<tr>
<td>LANDSCAPE</td>
<td>II</td>
<td>45</td>
<td>Active</td>
<td>Lapatinib + Capecitabine</td>
<td>60%</td>
</tr>
<tr>
<td>NALA</td>
<td>III</td>
<td>161</td>
<td>Stable</td>
<td>Neratinib + Capecitabine</td>
<td>21%</td>
</tr>
<tr>
<td>TBCRC-022</td>
<td>II</td>
<td>49</td>
<td>Active</td>
<td>Neratinib + Capecitabine</td>
<td>49% (Lapatinib-naive) 33% (prior Lapatinib)</td>
</tr>
<tr>
<td>PATRICIA</td>
<td>II</td>
<td>39</td>
<td>Active</td>
<td>Pertuzumab + High dose Trastuzumab</td>
<td>11%</td>
</tr>
<tr>
<td>NERERT-TX</td>
<td>II</td>
<td>29</td>
<td>Asymptomatic</td>
<td>Paclitaxel + Neratinib</td>
<td>Not reported; CNS incidence 0</td>
</tr>
</tbody>
</table>

*reference list Adapted from O’Brian B et al. SABCS 2022

3. Hurvitz SA, 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. Pérez-García JM, Vaz Batista M, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-
Leptomeningeal Carcinomatosis: Therapy

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

Review:

Systemic therapy

Methotrexat:
2. Glantz MJ, Jaeckle KA, Chamberlain MC et al.: A randomized controlled trial comparing intrathecal sustained-release cytarabine...


MTX high dose

Trastuzumab intrathecal.


Radiotherapy (Craniospinal irradiation):
Intrathecal administration of Trastuzumab

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

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