

Table 1. Characteristics of included studies – Systemische therapie bij hersenmetastasen mammacarcinoom

Study	Participants	Inclusion criteria brain metastases	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
<i>Systemic therapy for brain metastases from breast cancer previously treated with radiotherapy</i>							
<i>Patients regardless of hormone receptor and HER2 status</i>							
Tripathy, 2022 ATTAIN	N at baseline Intervention: n: 92 Control: 86 Age (median, range) Intervention: n: 53 (27-79) Control: 52 (24-77)	Symptomatic/asymptomatic brain metastases: Asymptomatic Prior treatment for brain metastases: 26% pts with combination of local therapies (whole-brain radiotherapy, stereotactic radiosurgery, and/or surgery) ≥14 days before randomization 74% pts with a single-agent modality (whole-brain radiotherapy, stereotactic radiosurgery, and/or surgical resection alone) if combination therapy was contraindicated ≥7	Intervention: Ertinotecan pegol (145 mg/m ² intravenously every 21 days on day 1 of each treatment cycle). Control: Physician's choice of chemotherapy every 21-28 days (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nabpaclitaxel).	N.S.	Overall survival Toxicity: Adverse events (grade 3 / 4) Treatment discontinuation Adverse events leading to death Progression-free survival Intracranial response: Complete response Partial response	Funding by industry (Nektar Therapeutics). ^{1, 2}	Some concerns (overall survival) High (toxicity) Some concerns (progression-free survival) High (intracranial response)

		days before randomization.					
		Size brain metastases: N.S.					
		Corticosteroid use: N.S.					
Cortés, 2017** BEACON trial	N at baseline Intervention: n: 36 Control: 31 Age (mean, range) Intervention: n: 54.5 (28-75) Control: 54.0 (37-76)	Symptomatic/asymptomatic brain metastases: Asymptomatic at least 28 days prior to randomization Prior treatment for brain metastases: 94.4% pts with local therapy (surgery, whole brain and/or stereotactic radiation) Size brain metastases: N.S. Corticosteroid use: Corticosteroids	Intervention: EP: topoisomerase-1 inhibitor Etrirnotecan pegol, 145 mg/m ² NKTR-102 will be delivered 21day as a 90 minute intravenous (IV) infusion on day 1 of each treatment cycle. Control: TPC: physicians choice single-drug treatment (eribulin, vinorelbine, gemcitabine, nab-paclitaxel, paclitaxel,	Time frame: 36 months Intervention: median 21.1 months Control: median 21.7 months	Overall survival Toxicity: Adverse events Treatment discontinuation Progression-free survival Intracranial response: Objective response rate	Funding by industry (Nektar Therapeutics). ⁴	Low (overall survival) Some concerns (toxicity) Some concerns (progression-free survival) High (intracranial response)

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		discontinued ≥3 weeks prior to randomization	ixabepilone, or docetaxel)				
<i>Patients with HER-2 positive cancer</i>							
André, 2023**	number of patients with brain metastases at baseline	Symptomatic/asymptomatic brain metastases: Asymptomatic	Intervention: Trastuzumab deruxtecan (intravenously at 5.4 mg/kg once every 3 weeks).	N.S.	Progression-free survival	Funding by industry (Daiichi Sankyo and AstraZeneca). ^{1,2,3}	Low (progression-free survival)
DESTINY-Breast02	Intervention: n: 74 Control: 36	Prior treatment for brain metastases: (number pts unknown) Whole-brain radiotherapy or stereotactic radiation therapy	Control: treatment of physician's choice. Either capecitabine (1250 mg/m ² ; orally twice daily			The study initially allowed enrolment of patients with previously untreated and asymptomatic brain metastases; however, during enrolment the protocol was amended to prohibit inclusion of patients with active brain metastases.	
		Size brain metastases: N.S.	on days 1–14) plus trastuzumab (8 mg/kg intravenously on day 1, then 6 mg/kg once per day) or capecitabine				
		Corticosteroid use: Those not requiring corticosteroids or anticonvulsants at inclusion were eligible	(1000 mg/m ²) plus lapatinib (1250 mg orally once daily on days 1–21).				

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Cortés, 2015	N at baseline	Symptomatic/asymptomatic brain metastases: N.S.	Intervention arm A: Afatinib alone (40 mg orally once per day) for 3 weeks, escalated to 50 mg if well tolerated.	Primary outcome: patient benefit at 12 weeks	Overall survival	Funding by industry (Boehringer Ingelheim) ^{1,2,3}	Low (overall survival)
LUX-Breast 3	Intervention A: 40 Intervention B: 37 Control C: 42	Prior treatment for brain metastases: 85% pts with systemic therapy and/or radiation therapy	Intervention arm B: Afatinib (40 mg per day) plus vinorelbine (25 mg/m ² once per week) in a 3-week cycle.	Trial total: 20-34 months	Toxicity: Adverse events		Some concerns (toxicity)
	Age (median, IQR)	Size brain metastases: ≥10 mm	Control arm C: Investigator's choice (any chemotherapy or medical treatment approved for advanced or metastatic breast cancer) for 3 weeks.		Progression-free survival		Some concerns (progression-free survival)
	Intervention A: 53 (43-58) Intervention B: 38 (44-57) Control C: 51 (44-63)	Corticosteroid use: No increase in corticosteroid dose Other: Absence of CNS disease progression according to RECIST version 1.1, no tumor-related worsening of neurological signs or symptoms. ("decline of two or more Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 levels for at least 7			Intracranial response: Objective response Disease control (CNS lesions)		High (intracranial response)

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		days for a neurological sign or symptom as neurological deterioration, unless it was attributable to comorbid events or changes in corticosteroid dose")					
Hurvitz, 2024** <i>DESTINY-Breast02</i>	number of patients with brain metastases at baseline Intervention: n: 43 Control: 39 Age (mean, range) Intervention: 52.8 (29.2-76.2) Control: 51.8 (26.0-78.2) Sex (% female)	Symptomatic/asymptomatic brain metastases: Asymptomatic at least for 14 days prior to randomization Prior treatment for brain metastases: 53.5% pts with local therapy (radiotherapy or surgery) to brain metastasis was mandatory Size brain metastases: N.S. Corticosteroid use: Those not requiring corticosteroids or anticonvulsants were	Intervention: Trastuzumab deruxtecan (intravenously 5.4 mg/kg every 3 weeks) Control: Trastuzumab emtansine (intravenously 3.6 mg/kg every 3 weeks)	Median duration of follow-up (months) Intervention: 16.2 (range 0-32.7) Control: 15.3 (range 0-31.3)	Progression-free survival Intracranial response: Objective response rate	Funding by industry (AstraZeneca and Daiichi Sankyo). ^{1,2,3}	Low (progression-free survival) High (intracranial response)

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	Intervention: 100% Control: 97.4%	eligible (no further specified)					
Krop, 2015** <i>EMILIA</i>	N at baseline Intervention: 45 Control: 50 Age (median, range) Intervention: 51 (27-71) Control: 53 (34-80) Race Intervention: 33.3% Asian Control: 16.0% Asian	Symptomatic/asymptomatic brain metastases: Asymptomatic (14 days after last radiotherapy treatment) and symptomatic (after radiotherapy only if symptom control was achieved ≥ 2 months prior to randomization). Prior treatment for brain metastases: 70% pts with radiotherapy Size brain metastases: N.S. Corticosteroid use: N.S.	Intervention: Lapatinib + capecitabine (orally 1250 mg daily every 21 days + orally 1000 mg/kg twice-daily on days 1-14 of each 21-day treatment cycle) Control: Trastuzumab emtansine (intravenously 3.6 mg/kg every 21 days)	N.S.	Overall survival Toxicity: Grade ≥ 3 adverse events Treatment discontinuation Time to neurological symptoms/neurocognitive decline Progression-free survival	Funding by industry (Genentech, Inc., Roche Group) ^{1,2,3}	Low (overall survival) Some concerns (toxicity) High (time to neurological symptoms/neurocognitive decline) Some concerns (progression-free survival)

	<p>Hormone-receptor positive cancers</p> <p>Intervention: 55.6%</p> <p>Control: 46.0%</p> <p>Prior radiotherapy for CNS metastases</p> <p>Intervention: 51.1% WBRT</p> <p>Control: 60.0% WBRT</p>						
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Lin, 2011	<p>N at baseline</p> <p>Intervention: 13</p> <p>Control: 9</p>	<p>Symptomatic/asymptomatic brain metastases: N.S.</p> <p>Prior treatment for brain metastases: 100% pts with whole-brain radiotherapy and/or stereotactic</p>	<p>Intervention: Lapatinib plus capecitabine (1250 mg orally daily + 2,000 mg/m² orally twice-daily on days 1-14 of a 21-day cycle)</p>	<p>Patients enrolled</p> <p>May 2007- Dec 2008.</p> <p>In June 2008, the study stopped enrolling patients for the intervention group, and permanently stopped in August 2008.</p>	<p>Toxicity:</p> <p>Adverse events (grade 3 / 4)</p> <p>Treatment discontinuation</p> <p>Intracranial response:</p> <p>Complete response</p> <p>Partial response</p>	<p>Funding by industry (GlaxoSmithKline) and non-profit organizations (Breast Cancer Research Foundation and American</p>	<p>Some concerns (toxicity)</p> <p>Low (intracranial response)</p>
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	Age (mean, range) Intervention: n: 49 (38-63) Control: 55 (37-69)	radiosurgery, and trastuzumab exposure Size brain metastases: ≥10 mm Corticosteroid use: Corticosteroid use was allowed at inclusion, concurrent use of enzyme inducing anti-epileptic agents was prohibited.	Control: Lapatinib plus topotecan (1250 mg daily + 3.2 mg/m ² intravenously on days 1, 8, and 15 of a 28-day cycle)			Society of Clinical Oncology Cancer Foundation) ^{1,2}	
Murthy, 2020 <i>HER2CLIMB</i> (Secondary analyses reported Curigliano (2021; Mueller (2021))	N at baseline Intervention: n: 198 Control: 93 Age (mean, SD) Intervention: n: 17% ≥65 years Control: 84% <65 years	Symptomatic/asymptomatic brain metastases: Symptomatic and asymptomatic Prior treatment for brain metastases: Untreated and treated. If patients required immediate local intervention, they could receive local therapy and enroll later.	Intervention: Tucatinib (300 mg orally twice-daily) plus trastuzumab (6 mg/kg intravenously once every 21 days) and capecitabine (1000 mg/m ² orally twice-daily on days 1-14 of each 21-day cycle). Control: placebo (orally twice-daily) plus trastuzumab and	N.S.	Overall survival (Curigliano, 2021) Quality of life (Mueller, 2021) Progression-free survival (Murthy, 2020) Intracranial response: Objective response rate (Murthy 2020)	Funding by industry (Seattle Genetics) ^{1,2,3}	Low (quality of life) Low (progression-free survival) Low (intracranial response)

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		Size brain metastases: Patients with untreated brain metastases >2 cm could enroll with approval from the medical monitor. Corticosteroid use: N.S.	Capecitabine (same dose as intervention group).				
<i>Combination of systemic therapy with concurrent radiotherapy for brain metastases from breast cancer</i>							
Cao, 2015	N at baseline Intervention: 50 Control: 50 Age (mean, range) Intervention: 57.8 (38-79) Control: 53.6 (29-78)	Symptomatic/asymptomatic brain metastases: Symptomatic and asymptomatic Prior treatment for brain metastases: No prior radiosurgery was allowed, and no specific prior systemic treatment lines needed to be given. Size brain metastases: N.S.	Intervention: Whole-brain radiotherapy (3 Gy x 10-30 Gy) + temozolomide (75mg/m ² /day during the radiation period for a total of 14 days) Control: Whole-brain radiotherapy (3 Gy x 10-30 Gy)	Max. 2-year Median follow-up (months) 9.4 (range 1.0-68.1)	Overall survival Toxicity Intracranial response: Objective response rate Progression-free survival	Funding by industry (Schering-Plough France). ⁴ Incomplete outcome data Intervention: N= 13 (26%) Reasons: 10 died before the first assessment at 6 weeks, 2 lost-to follow up, 1 discontinued because of tumor progression	Some concerns (overall survival) Some concerns (toxicity) High (intracranial response) Some concerns (progression-free survival)

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		<p>Corticosteroid use: Corticosteroids and antiepileptic drugs</p> <p>were prescribed at the lowest dosage, when necessary.</p>				<p>Control:</p> <p>N= 3 (6%)</p> <p>Reasons: 3 died before the first assessment at 6 weeks</p>	
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**For further details, see risk of bias table in the appendix*

**** Subgroup analysis**

¹ *Funder supplied study drugs;*

² *Funder had a role in the study conduct;*

³ *Authors, including first/last author, were involved with the funders of the study (e.g., advisory board);*

⁴ *Role of the funder: not stated.*