Summary of Findings – Systemische therapie bij hersenmetastasen mammacarcinoom

1.2 Systemic therapy for brain metastases from breast cancer previously treated with radiotherapy

Population: Patients with brain metastases from breast cancer, previously treated locally (radiotherapy and/or resection)
Intervention: Systemic therapy
Comparator: Other systemic therapy, repeated RT

	Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Conclusions
			Control	Intervention		
André, 2023** DESTINY-Breast02			Investigator's choice	Trastuzumab deruxtecan		
	Progression-free survival (important)	Median PFS (months) Intervention: 13.9 (95% CI 11.1 -18.0) Control: 5.6 (95% CI 3.3- 8.1) HR 0.35 (0.20-0.61)	-	-	Low[1]	Trastuzumab deruxtecan may increase PFS compared to treatment of investigator's choice (capecitabine + trastuzumab/lapatinib) in patients with brain metastases from breast cancer.
Cortés, 2015 LUX-Breast 3			C: Investigator's choice	A: Afatinib B: Afatinib + vinorelbine		
	Overall survival (critical)	Median OS (weeks) A: 57.7 (95% CI 39.3- 68.1), B: 37.3 (95% CI 25.3- 57.3), C: 52.1 (95% CI 39.3-80.4) A vs C: HR 1.27 (95% CI 0.72-2.21, p=0.41) B vs C: HR 1.60 (95% CI 0.93-2.76, p=0.09)	-	-	Very low[2]	The evidence is very uncertain about the effect of afatinib alone or combined with vinorelbine on OS in patients with brain metastases from breast cancer.

	Toxicity (critical)	RR: A: 0.36 (95% CI 0.08-1.67) B: 0.75 (95% CI 0.23-2.47)	Treatment discontinuation due to adverse events: C: 6/43 (14.0%)	Treatment discontinuation due to adverse events: A: 2/40 (5.0%) B: 4/38 (10.5%)	Very low[3]	The evidence is very uncertain about the effect of afatinib alone or combined with vinorelbine on toxicity in patients with brain metastases from breast cancer.
	Progression-free survival (important)	Median PFS (weeks) A: 11.9 (95% CI 6.3- 18.7) B: 12.3 (95% CI 7.4- 17.3) C: 18.4 (95% CI 11.1- 21.1) A vs C: HR 1.18 (95% CI 0.72-1.93, p=0.51) B vs C: HR 0.94 (95% CI 0.57-1.54, p=0.78)	-	-	Very low[4]	The evidence is very uncertain about the effect of afatinib alone or combined with vinorelbine on PFS when compared with treatment of investigator's choice in patients with brain metastases from breast cancer.
	Intracranial response (important)	RR ORR: A: 0.08 (95% CI 0.00-1.42) B: 0.57 (95% CI 0.15-2.11) RR disease control: A: 0.94 (95% CI 0.70-1.24) B: 0.99 (95% CI 0.75-1.30)	ORR: C: 6/43 (14%) Disease control (CNS lesions) C: 31/43 (72%)	ORR: A: 0 B: 3/38 (8%) Disease control (CNS lesions) A: 27/40 (68%) B: 27/38 (71%)	Very low[5]	The evidence is very uncertain about the effect of afatinib alone or combined with vinorelbine on intracranial response in patients with brain metastases from breast cancer.
			Investigator's choice	Etirinotecan pegol		

Cortés, 2017** BEACON trial	**Overall survival** (critical)	Median OS (months) Intervention: 10.0 (95% CI 7.8-15.7) Control: 4.8 (95% CI 3.7-7.3) HR 0.51 (95% CI 0.30-0.86, p<0.01) *Subgroup stable brain metastases on baseline imaging (Fig.1C)* Median OS months Intervention (n = 19): 13.2 (8.6-19.6) Control (n = 18): 5.8 (3.5-8.6) HR 0.45 (95% CI 0.22-0.92, p=0.02)	-	-	Low[6]	Etirinotecan pegol may increase OS compared to treatment of investigator's choice in patients with brain metastases from breast cancer.
	Toxicity (critical)	RR AEs: 0.71 (95% CI 0.47-1.08) RR treatment discontinuation: 0.18 (95% CI 0.02-1.37)	AEs (grade 3 / 4 / 5): 19/27 (70.4%) Treatment discontinuation (attributed to an AE): 1/27 (3.7%)	AEs (grade 3 / 4 / 5): 17/34 (50%) Treatment discontinuation (attributed to an AE): 7/34 (20.6%)	Very low[7]	The evidence is very uncertain about the effect of etirinotecan pegol on toxicity when compared to treatment of investigator's choice in patients with brain metastases from breast cancer.
	Progression-free survival (important)	Median PFS (months) Intervention: 3.1 (1.8-4.0) Control: 2.7 (1.8- 3.7) HR 0.84 (95% CI 0.49-1.43, p=0.52)	-	-	Very low[8]	The evidence is very uncertain about the effect of etirinotecan pegol on PFS when compared with treatment of investigator's choice in patients with

						brain metastases from breast cancer.
	Intracranial response (important)	RR 4.31 (95% CI 0.53-34.90)	ORR: 1/31 (3.7%) (95% CI 0.1-19.0)	ORR: 5/36 (15.6%) (95% CI 5.3-32.8)	Very low[9]	The evidence is very uncertain about the effect of etirinotecan pegol on intracrianial response when compared with treatment of investigator's choice in patients with brain metastases from breast cancer.
Hurvitz, 2024**			Trastuzumab emtansine	Trastuzumab deruxtecan		
DESTINY-Breast03	**Progression-free survival** (important)	Median PFS (months) Intervention: 15.0 (95% CI 12.5-22.2) Control: 3.0 (95% CI 2.8-5.8) HR 0.25 (95% CI 0.13-0.45).	-	-	Very low[10]	The evidence is very uncertain about the effect of trastuzumab deruxtecan pegol on PFS when compared with trastuzumab emtansine in patients with brain metastases from breast cancer.
	Intracranial response (important)	RR: 3.29 (95% CI 1.71-6.31)	ORR: 8/39 (20.5%) (95% CI 9.3-36.5)	ORR: 29/43 (67.4%) (95% CI 51.5-80.9)	Low[11]	Trastuzumab deruxtecan pegol may improve intracranial response when compared with trastuzumab emtansine in patients with brain metastases from breast cancer.
Krop, 2015**			Trastuzumab emtansine	Lapatinib + capecitabine		

EMILIA	**Overall survival** (critical)	Median OS (months) Intervention: 12.9 Control: 26.8 HR = 0.38 (95% CI 0.18-0.80, p= 0.008)	-	-	Low[12]	The evidence suggests that lapatinib + capecitabine may result in a lower OS compared to trastuzumab emtansine in patients with brain metastases from breast cancer.
	Toxicity (critical)	RR grade ≥ 3 AEs: 0.77 (95% CI 0.53-1.12) RR treatment discontinuation: 0.19 (95% CI 0.02-1.52)	Grade ≥ 3 AEs: 21/43 (48.8%) Treatment discontinuation: 1/43 (2.3%)	Grade ≥ 3 AEs: 31/49 (63.3%) Treatment discontinuation: 6/49 (12.2%)	Very low[13]	The evidence is very uncertain about the effect of lapatinib + capecitabine on toxicity when compared with trastuzumab emtansine in patients with brain metastases from breast cancer.
	Time to neurological symptoms/neurocognitive decline (critical)	Median time-to-symptom progression (months) Intervention: 5.5 Control: 7.2 HR = 0.70 (95% CI 0.33-1.48, p = 0.338)	CNS progression: 10/45 (22.2%)	CNS progression: 10/45 (22.2%) CNS progression: 8/50 (16.0%)	Very low[14]	The evidence is very uncertain about the effect of lapatinib + capecitabine on time to neurological symptoms/neurocognitive decline when compared with trastuzumab emtansine in patients with brain metastases from breast cancer.
	Progression-free survival (important)	Median PFS (months) Intervention: 5.7 Control: 5.9	-	-	Very low[15]	The evidence is very uncertain about the effect of lapatinib + capecitabine on PFS when compared with trastuzumab emtansine in patients with

		HR = 1.00 (95% CI 0.54-1.84, p= 1.00)				brain metastases from breast cancer.
Lin, 2011			Lapatinib + capecitabine	Lapatinib + topotecan		
	Toxicity (critical)	RR treatment discontinuation: 0.14 (95% CI 0.01-2.66)	AEs (grade 3 / 4): 10/9 Treatment discontinuation (toxicity): 2/9	AEs (grade 3 / 4): 6/13 Treatment discontinuation (toxicity): 0/13	Very low[16]	The evidence is very uncertain about the effect of lapatinib + topotecan on PFS when compared with lapatinib + capecitabine in patients with brain metastases from breast cancer.
	Intracranial response (important)	RR: N.E.	CR: 0 PR: 0	CR: 0 PR: 5/13 (58%)	Very low[17]	The evidence is very uncertain about the effect of lapatinib + topotecan on intracranial response when compared with lapatinib + capecitabine in patients with brain metastases from breast cancer.
Murthy, 2020 *HER2CLIMB*			Placebo + trastuzumab and capecitabine	Tucatinib + trastuzumab and capecitabine		
	Overall survival (critical)	Intervention: 189/291 (65.0%) Control: N.S. HR: 0.60 (95% CI 0.44-0.81)	-	-	Low[18]	Adding tucatinib to trastuzumab and capecitabine may increase overall survival in patients with brain metastases from breast cancer.

	Quality of life (critical)	Time to meaningful deterioration (≥7 points) in the EQ-VAS score in HR-QoL Intervention: 26/107 (24.3%) Control: 20/56 (35.7%) HR: 0.51 (95% CI 0.28-0.93)	-	-	Low[19]	Adding tucatinib to trastuzumab and capecitabine may increase QoL in patients with brain metastases from breast cancer.
	Progression-free survival (important)	PFS at 1 year Intervention: 24.9% (95% CI: 16.5-34.3) Control: 0% Median PFS (months) Intervention: 7.6 (95% CI 6.2-9.5) Control: 5.4 (95% CI 4.1-5.7) HR: 0.48 (95% CI 0.34-0.69; P<0.001)	51/93	106/198	Low[20]	Adding tucatinib to trastuzumab and capecitabine may increase PFS in patients with brain metastases from breast cancer.
	Intracranial response (important)	RR ORR: 1.78 (95% CI 1.31-2.41)	ORR: 39/171 (22.8%) (95% CI 16.7-29.8) CR: 2/171 (1.2%) PR: 37/171 (21.6%)	ORR: 138/340 (40.6%) (95% CI 35.3-46.0) CR: 3/340 (0.9%) PR: 135/340 (39.7%)	Low[21]	Adding tucatinib to trastuzumab and capecitabine may increase intracranial response in patients with brain metastases from breast cancer.
Tripathy, 2022 *ATTAIN*			Investigator's choice	Etirinotecan pegol		
	Overall survival (critical)	Median OS (months) Intervention: 7.8 (95% CI 6.1-10.2)	-	-	Very low[27]	Etirinotecan pegol may result in little to no difference in OS when compared with treatment

		Control: 7.5 (95% CI 5.8-10.4) HR = 0.90 (95% CI 0.61-1.33); P = 0.60).				of investigator's choice in patients with brain metastases from breast cancer.
	Toxicity (critical)	RR AEs: 0.89 (95% CI 0.70-1.14) RR SAEs: 1.18 (95% CI 0.77-1.81) RR treatment discontinuation: 7.70 (1.00-59.42) RR AEs leading to death: N.E.	AEs (grade 3 / 4): 49/77 (63.6%) SAEs: 24/77 (31.2%) Treatment discontinuation: 1/77 (1.3%) AEs leading to death: 0.0%	AEs (grade 3 / 4): 51/90 (56.7%) SAEs: 33/90 (36.7%) Treatment discontinuation: 9/90 (10.0%) AEs leading to death: 3/90 (3.3%)	Very low[28]	Etirinotecan pegol may result in little to no difference in toxicity when compared with treatment of investigator's choice in patients with brain metastases from breast cancer.
	Progression-free survival (important)	Median PFS (months) Intervention: 3.9 (2.6-4.3) Control: 3.3 (1.9-3.7) HR = 0.59 (95% CI 0.33-1.05); P = 0.07).	-	-	Very low[29]	Etirinotecan pegol may result in little to no difference in PFS when compared with treatment of investigator's choice in patients with brain metastases from breast cancer.
	Intracranial response	RR PR: 1.87 (95% CI 0.35-9.95)	CR: 0 PR: 2/86 (2.7%)	CR: 0 PR: 4/92 (4.8%)	Very low[30]	Etirinotecan pegol may result in little to no difference in intracranial

	(important)					response when compared with treatment of investigator's choice in patients with brain metastases from breast cancer.

AE: adverse event; CNS: central nervous system; CR: complete response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; SAE: serious adverse event.

** Subgroup analysis

[1] **Risk of bias**: **serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision**: **serious.** Low number of patients, optimal information size not achieved.

[2] **Risk of bias: serious.** Role of the funder. **Imprecision**: **very serious.** Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[3,4,5] **Risk of bias**: **serious**. Due to lack of blinding. **Imprecision**: **very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[6] **Risk of bias**: **serious.** Subgroup analysis, allocation concealment questionable. **Imprecision**: **serious.** Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference.

[7,8] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable. **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[9] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable. **Imprecision: very serious**. Due to extremely broad 95% CI overlap.

[10] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision**: **very serious.** Low number of patients, optimal information size not achieved. Ratio upper/lower bound of 95% CI > 3 RR.

[11] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision: serious**. Broad 95% CI.

[12] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision: serious**. Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference.

[13, 14, 15] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[16] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision: very serious**. Ratio upper/lower bound of 95% CI > 3 RR.

[17] **Risk of bias: serious.** Subgroup analysis, allocation concealment questionable and role of the funder. **Imprecision: serious**. Low number of patients, not possible to calculate risk ratio.

[18, 19] **Risk of bias: serious**. Role of the funder. **Imprecision: serious**. Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference.

[20, 21] **Risk of bias: serious**. Role of the funder. **Imprecision: serious**. Low number of patients, optimal information size not achieved.

[22] **Risk of bias: serious**. Role of the funder. **Imprecision: very serious**. Due to low patient number.

[23, 24] **Risk of bias: serious.** No allocation concealment. **Imprecision: very serious**. Ratio upper/lower bound of 95% CI > 3 RR.

[25] **No GRADE.**

[26] **Risk of bias: serious.** No allocation concealment. **Imprecision: very serious**. Ratio upper/lower bound of 95% CI > 3 RR.

[27] **Risk of bias: serious**. Role of the funder. **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[28] **Risk of bias: serious.** No allocation concealment and role of the funder. **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[29, 30] **Risk of bias: serious.** No allocation concealment and role of the funder. **Imprecision: very serious**. Ratio upper/lower bound of 95% CI > 3 RR.

1.3 Combination of systemic therapy with concurrent radiotherapy for brain metastases from breast cancer

Population: Patients with brain metastases from breast cancer, previously treated locally (radiotherapy and/or resection)
Intervention: Systemic therapy + RT
Comparator: Other systemic therapy, repeated RT

	Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Conclusions
			Control	Intervention		
Cao (2015)			WBRT	WBRT + temozolomide		
	Overall survival (critical)	Median OS (months) Intervention: 9.4 (95% CI 7.3-13.4) Control: 11.1 (95% CI 8.3-15.3) HR 0.91 (0.62-1.35)	-	-	Low[1]	WBRT + temozolomide may result in little to no difference in OS when compared with WBRT alone in patients with brain metastases from breast cancer.
	Toxicity (critical)	RR 1.35 (0.83-2.21)	17/50 (34%)	23/50 (46%)	Very low[2]	The evidence is very uncertain about the effect of WBRT + temozolomide on toxicity when compared with WBRT alone in patients with brain metastases from breast cancer.
	Progression-free survival (important)	Median PFS (months) Intervention: 6.8 (95% CI 4.6-8.6) Control: 7.4 (95% CI 5.3-13.1) HR 1.07 (0.75-1.53)	-	-	Low[3]	WBRT + temozolomide may result in little to no difference in PFS when compared with WBRT alone in patients with brain metastases from breast cancer.

	Intracranial response (important)	RR 0.83 (0.48-1.46)	ORR: 18/50 (36%)	ORR: 15/50 (30%)	Very low[4]	The evidence is very uncertain about the effect of WBRT + temozolomide on intracranial response when compared with WBRT alone in patients with brain metastases from breast cancer.

CI: confidence interval; HR: hazard ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RR: relative risk; WBRT: whole-brain radiotherapy.

[1] **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference.

[2] **Risk of bias: serious.** No allocation concealment. **Imprecision: very serious**. Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference.

[3] **Risk of bias: serious.** No allocation concealment. **Imprecision: serious**. Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference.

[4] **Risk of bias: serious.** No allocation concealment. **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference