Summary of Findings – Systemische therapie bij hersenmetastasen longcarcinoom

Subquestion 1: What is the effectivity of systemic therapy on brain metastases from lung carcinoma not previously treated locally?
Population: Patients with brain metastases from lung carcinoma, not previously treated locally
Intervention: Systemic therapy
Comparator: Other systemic therapy, radiotherapy or expectative policy

	Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
			Control	Intervention		
Presence of AGA						
EGFR mutatie						
Park, 2016	**Progression-free survival** (important)	Months (median, 95% CI) Intervention: 7.2 (3.7–19.0) Control: 7.4 (5.4-12.8) HR: 0.76 (0.41-1.44)	Gefinitib	Afatinib		
					Very Low[1]	The evidence is very uncertain about the effect of Afatinib when compared with Gefinitib in patients with brain metastases from lung cancer.
Yang, 2017	**Overall Survival** (crucial)	Median (months) Intervention: 18.0 Control: 20.5 HR: 0.93 (95% CI, 0.60-1.44), *p*=0.734	WBRT + chemo	Icotinib	Very Low[2]	The evidence is very uncertain about the effect of Icotinib on OS when compared with WBRT + chemo in patients with brain metastases from lung cancer.
			-	-		

	Progression-free survival (important)	Median (months) Intervention: 6.8 Control: 3.4 HR: 0.44 (95% CI, 0.31-0.63), *p*<0,0001			Very Low[3]	The evidence is very uncertain about the effect of Icotinib on PFS when compared with WBRT + chemo in patients with brain metastases from lung cancer.

[1] **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. Low number of patients, optimal information size not achieved.
[2] **Risk of bias: serious.** Allocation concealment questionable, role of the funder. **Imprecision**: **very serious.** Due to overlap of both limits of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[3] **Risk of bias: serious.** Allocation concealment questionable, role of the funder. **Imprecision**: **very serious.** Due to overlap of lower limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.

Subquestion 2: What is the effectivity of systemic therapy on brain metastases from lung carcinoma that have previously been treated locally?
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		
Presence of AGA						
EGFR-mutatie						
Yu, 2022 (Keynote189, Checkmate9LA	**Overall Survival** (crucial)		Control	Intervention		Pembrolizumab+pemetrexed+cisplatin/carboplatin may increase OS compared with Pemetrexed+cisplatin/ Carboplatin in patients with brain metastases

		HR: 0.71 (95% CI, 0.53-0.94)			Low[4]	from nonsquamous NSCLC (HR: 0.41; 95%CI, 0.24-0.67). (KEYNOTE-189) Nivolumab+ipilimumab+ platinum doublet may increase OS compared with histology-based, platinum doublet chemotherapy in patient with brain metastases from NSCLC(HR: 0.38; 95%CI, 0.24-0.60). (Checkmate 9LA)
				-	Low[4]	
	Progression-free survival (important)	HR: 0.53 (95% CI, 0.40-0.69)			Low[4]	Pembrolizumab+pemetrexed+cisplatin/carboplatin may increase PFS compared with pemetrexed+cisplatin/ carboplatin in patients with brain metastases from nonsquamous NSCLC (HR: 0.42; 95%CI, 0.27-0.67). (KEYNOTE-189)

						Nivolumab+ipilimumab+ platinum doublet may increase PFS compared with histology-based, platinum doublet chemotherapy in patient with brain metastases from NSCLC (HR: 0.42; 95%CI, 0.28-0.65). (Checkmate 9LA) Sugemalimab+carboplatin + paclitaxel/pemetrexed may increase PFS compared with placebo+carboplatin+paclitaxel/pemetrexeds (HR: 0.29; 95%CI,0.15-0.56) in patients with brain metastases from NSCLC (Gemstone-302)
1.1.2 ALK translocatie						
Zheng, 2023 (J-ALEX;ALEX;ALESIA;ALUR;ALTA-1L;CROWN;eXalt3	**Progression-free survival** (important)	HR: 0.36 (95% CI, 0.26-0.50)	Placebo, chemotherapy, another ALKis	ALKis (crizotinib, alectinib, brigatinib, lorlatinib, ensartinib, and chemotherapy)	Low[5]	Alectinib may increases PFS compared to other AKIs (HR: 0.17; 95%CI, 0.07-0.37); other AKIs may increase PFS compared to Crizotinib (HR: 0.33; 95%CI, 0.19-0.56) in patients with brain

						metastases from lung cancer.

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

[5] **Risk of bias**: **serious.** Subgroup analysis, allocation concealment questionable and role of the funder **Imprecision**: **serious.** Due to overlap of the lower limit of the 95% CI with the minimal clinically important difference. Due to Low number of patients, optimal information size not achieved.

	Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
			Control	Intervention		
1.1 Presence of AGA						
1.1.1 EGFR mutatie						
Schuler, 2016	**Overall Survival** (crucial)	Median (months) Lux-Lung 3 Intervention: 19.8 Control: 33.2 Lux-Lung 6: Intervention: 22.4 Control: 24.7 p= 0.732 Lux-Lung 3+6 Intervention: 22.4	Intravenous platinum-based chemotherapy (LUX-Lung 3 Gemcitabine (Lux-Lung 6)	Afatinib	Very Low[6]	The evidence is very uncertain about the effect of afatinib on OS when compared with Intravenous platinum-based chemotherapy or gemcitabine in patients with brain metastases from NSCLC.

		Control: 25.0 HR: 1.14 (95% CI, 0.66 – 1.94), p=0.641				
	Progression-free survival (important)	Median (months) Lux-Lung 3: Intervention: 11.1 Control: 5.4 HR: 0.54 (95% CI, 0.23-1.25), p=0.138 Lux-Lung 6: Intervention: 8.2 Control: 4.7 HR: 0.47 (95% CI, 0.18-1.21), p=0.11 Lux-Lung 3 + 6 (pooled) Intervention: 8.2 Control: 5.4 HR: 0.50 (95% CI, 0.27 – 0.95), *p=0.03*			Very Low[7]	The evidence is very uncertain about the effect of Afatinib on PFS when compared with Intravenous platinum-based chemotherapy or gemcitabine in patients with brain metastases from NSCLC.
Reungwetwattana, 2018	**Progression-free survival** (important)	CNS PFS, median (months, 95% CI) Intervention: NR (16.5 to NC) Control: 13.9 (8.3 to NC) HR: 0.48 (95% CI, 0.26-0.86), p=0.01	Standard oral EGFR-TKI (gefitinib or erlotinib)	Osimertinib	Very Low[7]	The evidence is very uncertain about the effect of Osimertinib on PFS when compared with Standard oral EGFR-TKI in patients with brain metastases from NSCLC.

1.1.2 ALK translocatie						
Peters, 2017	**Progression-free survival** (important)	HR: 0.40 (95% CI, 0.25-0.64)	Crizotinib	Alectinib	Very Low[8]	The evidence is very uncertain about the effect of Alectinib on PFS when compared with Crizotinib in patients with brain metastases from NSCLC.
Soloman, 2016	**Progression-free survival** (important)	Median (months, 95% CI) Intervention: 9.0 (6.8-15.0) Control: 4.0 (1.5-6.8) HR: 0.40 (0.23-0.69)	Chemotherapy	Crizotinib	Very Low[9]	The evidence is very uncertain about the effect of crizotinib on PFS when compared with Chemotherapy in patients with brain metastases from NSCLC.
Camidge, 2018	**Progression-free survival** (important)	Intervention: NR (11-NR) Control: 5.6 (4.1-9.2) HR: 0.27 (95% CI, 0.13-0.54)	Crizotinib	Brigatinib	No Grade	No evidence is found regarding the effect of Brigatinib on PFS when compared with Crizotinib in patients with brain metastases from NSCLC.
Shaw, 2017 Soria, 2017	**Progression-free survival** (important)	HR: 0.58 (95% CI, 0.42-0.80)	Chemotherapy	Ceritinib	Very Low[9]	The evidence is very uncertain about the effect of Ceritinib on PFS when compared with Chemotherapy in

						patients with brain metastases from NSCLC.
Edelman, 2010	**Overall Survival** (crucial)	Median (months, 95% CI) Arm 1 versus arm 3: 0.97 (0.68–1.40), *p*=0,89 Arm 2 versus arm 3: 0.94 (0.65–1.36), *p*=0.74		Arm 1: gemcitabine + carboplatin Arm 2: gemcitabine + paclitaxel	Very Low[10]	The evidence is very uncertain about the effect of gemcitabine + carboplatin on OS when compared with gemcitabine + paclitaxel in patients with brain metastases from NSCLC.
	Progression-free survival (important)	Median (HR, 95% CI) Arm 1 versus arm 3: 0.92 (0.64–1.33), *p*=0.67 Arm 2 versus arm 3: 1.06 (0.74–1.54), *p*=0.74			Very Low[10]	The evidence is very uncertain about the effect of gemcitabine + carboplatin on OS when compared with gemcitabine + paclitaxel in patients with brain metastases from NSCLC.

[6] **Risk of bias: very serious.** Subgroup analysis, allocation concealment questionable and role of funder. **Imprecision: very serious**. Due to overlap of both limits of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[7] **Risk of bias: very serious.** Subgroup analysis, allocation concealment questionable and role of funder. **Imprecision: very serious**. Due to overlap of the lower limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[8] **Risk of bias: very serious.** Subgroup analysis, missing outcome data, role of the funder, conflict of interest authors. **Imprecision**: **Serious.** Low number of patients, optimal information size not achieved.
[9] **Risk of bias: very serious.** Subgroup analysis, allocation concealment questionable, missing outcome data, role of the funder and conflict of interest authors. **Imprecision**: **serious.** Due to low number of patients, optimal information size not achieved.
[10] **Risk of bias: serious.** Allocation concealment questionable and conflict of interest authors. **Imprecision**: **very serious.** Due to overlap of both limits of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.

Subquestion 4: What is the effectivity of systemic therapy with concurrent radiotherapy on brain metastases from lung carcinoma?
Population: Patients with brain metastases from breast cancer, not previously treated locally (radiotherapy and/or resection)
Intervention: Systemic therapy + RT
Comparator: Only systemic therapy, only radiotherapy, other systemic therapy with concurrent radiotherapy

	Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
			Control	Intervention		
No known AGA						
Lim, 2014	**Overall Survival** (crucial)	Median (months, 95% CI) Intervention: 14.6 (9.2-20.0) Control: 15.3 (7.2-23.4) HR: 1.2 (95%CI, 0.77-1.89), p=0.42	Chemotherapy	SRS + Chemotherapy	Very Low[11]	The evidence is very uncertain on the effect of SRS + Chemotherapy on OS when compared with chemotherapy in patients with brain metastases from NSCLC.
	Progression-free survival (important)	PFS intracranial disease (months, 95% CI) Intervention: 9.4 (4.2-14.6) Control: 6.6 (2.9-10.3) P=0.25			Low[12]	SRS + Chemotherapy may increase PFS incranial disease when compared with chemotherapy in patients with brain metastases from NSCLC.
Lee, 2008	**Overall Survival** (crucial)	Median Intervention: 3.4 Control: 2.9 HR (raw): 0.94 (95% CI, 0.58-1.54), p=0.81	Placebo + WBRT -	Erlotinib + WBRT -	Very Low[13]	The evidence is very uncertain about the effect of Erlotinib + WBRT on OS when compared with Placebo + WBRT in patients with brain metastases from NSCLC.

		HR (corrected): 0.95 (95% CI, 0.58-1.55)				
Lee, 2014	**Overall Survival** (crucial)	CNS PFS, median (months, 95% CI) Intervention: NR (16.5 to NC) Control: 13.9 (8.3 to NC) HR: 0.48 (95% CI, 0.26-0.86), p=0.01	Standard oral EGFR-TKI	Osimertinib	Very Low[14]	The evidence is very uncertain about the effect of Osimertinib on OS when compared with Standard oral EGFR-TKI in patients with brain metastases from NSCLC.
	Progression-free survival (important)	Neurological PFS, median (months) Intervention: 1.6 Control: 1.6			Low[15]	Osimertinib may result in little to no difference in PFS when compared with Standard oral EGFR-TKI in patients with brain metastases from NSCLC.
Quantin (2010)	**Overall Survival** (crucial)	Median (months, 95% CI) Intervention: 8.5 (6.4-10.8) Control: 5.7 (4.6-11.9) P=0.82	Crizotinib	Alectinib	Low[16]	Alectinib may increase OS when compared with Crizotinib in patients with brain metastases from NSCLC.
	Progression-free survival (important)	% (95% CI) 6 months: Intervention: 58% (40.7-75.4) Control: 30% (13.6-46.4) 12 months: Intervention: 19.3% (5.4-33.2) Control: 10% (0-20.7)	Chemotherapy	Crizotinib	No grade	No evidence is found regarding the effect of Crizotinib on PFS when compared with Chemotherapy

						in patients with brain metastases from NSCLC.
Guerrieri, 2004	**Overall Survival** (crucial)	Months (median, 95% CI) Intervention: 3.7 (2.7-5.8) Control: 4.4(2.0-5.1) P=0.64	WBRT	WBRT + Carboplatin	Very low[17]	The evidence is very uncertain about the effect of WBRT + Carboplatin on OS when compared with WBRT in patients with brain metastases from NSCLC.
Sperduto, 2013	**Overall Survival** (crucial)	Median (months, 95% CI) Arm 1: 13.4 (6.5-20.8) Arm 2: 6.3 (3.4-10.1) Arm 3: 6.1 (3.6-12.1) HR (adjusted): Arm 2 versus 1 1.46 (95% CI, 0.91–2.36), *p=0.*94 Arm 3 versus 1 1.46 (95% CI, 0.91–2.34), *p=0.*94)		Arm 1: WBRT +SRS Arm 2: WBRT + SRS + Temozolomide Arm 3: WBRT + SRS + Erlotinib	Very Low[18]	The evidence is very uncertain about the effect of WBRT + SRS on OS when compared with WBRT+ SRS + Temozolomide, and WBRT + SRS + Erlotinib in patients with brain metastases from NSCLC.
Pesce, 2012	**Overall Survival** (crucial)	Median (months, 95% CI) Intervention: 6.3 (2.1-14.6) Control: 4.9(2.3-5.6) 6 months (%, 95% CI) Intervention: 37.5% (15.4–59.8) Control: 20.9% (10.4–34.0)	WBRT + Temozolomide	WBRT + Gefinitub	Very Low[19]	The evidence is very uncertain about the effect of WBRT + Gefinitub on OS when compared with WBRT + Temozolomide in patients with brain metastases from NSCLC.

Chua, 2010	**Overall Survival** (crucial)	Median (months, 95% CI) Intervention: 4.4 Control: 5.7 P= 0.59 HR: 1.14 (95% CI, 0.71-1.83)	WBRT	WBRT + Temozolomide	very Low[20]	The evidence is very uncertain about the effect of WBRT + Temozolomide on OS when compared with WBRT in patients with brain metastases from NSCLC.
Small cell lung cancer						
Liu, 2010	**Overall Survival** (crucial)	Median (months, 95% CI) Intervention: 11 (8.82-13.18) Control: 10 (8.29-11.71) P> 0.05	Commitment RT and chemotherapy	Sequential RT and chemotherapy	Very Low[21]	The evidence is very uncertain about the effect of Sequential RT and chemotherapy on OS when compared with Commitment RT and chemotherapy in patients with brain metastases from small cell lung cancer.
Lung cancer, unspecified						
Neuhaus, 2010	**Overall Survival** (crucial)	HR: 1.32 (95% CI, 0.83-2.1)	WBRT	Topotecan + WBRT	Very Low [22]	The evidence is very uncertain about the effect of Topotecan + WBRT on OS when compared with WBRT in patients with brain metastases from lung cancer.

	Progression-free survival (important	HR: 1.28 (95% CI,0.73-2.43)			Very Low[22]	The evidence is very uncertain about the effect of Topotecan + WBRT on PFS when compared with WBRT in patients with brain metastases from lung cancer.

[11] **Risk of bias: very serious.** Allocation concealment questionable, blinding procedure unknown and role of funder. **Imprecision**: **very serious.** Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[12] **Risk of bias: serious.** Allocation concealment questionable, blinding procedure unknown and role of funder. **Imprecision: serious**. Low number of patients, optimal information size not achieved.
[13] **Risk of bias: very serious.** Allocation concealment questionable, blinding procedure unknown and role of funder. **Imprecision: very serious**. Due to overlap of both the limits of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[14] **Risk of bias: very serious.** Allocation concealment questionable, blinding procedure unknown, incomplete outcome data and role of funder. **Imprecision: very serious.** Due to overlap of the lower limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[15] **Risk of bias: very serious.** Allocation concealment questionable, blinding procedure unknown and role of funder. **Imprecision: very serious.** Due to overlap of the lower limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[16] **Risk of bias: serious.** Blinding procedure unknown and incomplete outcome data unknown. **Imprecision: serious.** Low number of patients, optimal information size not achieved.
[17] **Risk of bias: very serious.** Allocation concealment questionable, blinding procedure unknown, incomplete outcome data unknown and role of funder unknown. **Imprecision: serious.** Low number of patients, optimal information size not achieved.
[18] **Risk of bias: very serious.** Allocation concealment questionable, blinding procedure unknown, incomplete outcome data and role of funder. **Imprecision: serious.** Due to overlap of the lower limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[19] **Risk of bias: very serious.** Allocation concealment questionable, infrequent outcome data and role of funder. **Imprecision: serious.** Low number of patients, optimal information size not achieved.
[20] **Risk of bias: serious.** Allocation concealment questionable. **Imprecision: very serious.** Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.
[21] **Risk of bias: very serious**. Allocation concealment questionable, blinding procedure unknown and role of funder. **Imprecision: serious**. Due to low number of patients, optimal information size not achieved.
[22] **Risk of bias: very serious**. Allocation concealment questionable, blinding procedure unknown and role of funder. **Imprecision: very serious**. Due to overlap of the upper limit of the 95% CI with the minimal clinically important difference. Low number of patients, optimal information size not achieved.