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

Study	Participants	Inclusion criteria brain metastases	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Subquestion 1: Systemic therapy for brain metastases from lung cancer, no previous local treatment							
Park, 2016	N at baseline Intervention: 26 Control: 24 Histology: NSCLC	Presence of a driver mutation/translocation: EGFR-TKI Symptomatic/asymptomatic brain metastases: Asymptomatic Baseline characteristics not stratified by presence of brain metastases. Patients with brain metastases could only be included if the metastases were asymptomatic and there was no indication for local treatment at time of screening	Intervention: Afatinib (40 mg orally once a day) Control: Gefinitib (250 mg daily)	NR	PFS	Supported by Boehringer Ingelheim[4]	Some concerns
Yang, 2017	N at baseline Intervention: 85 Control: 91	Presence of a driver mutation/translocation: EGFR-TKI No prior treatment for brain metastases with radiotherapy	Intervention: Icotinib (124 mg, three times per day) Control: WBRT (30 Gy in ten fractions of 3 Gy) + concurrent or sequential	Mortality	OS PFS	Funded by Guangdong Provincial Key Laboratory of Lung Cancer Translational Medicine, National Health and Family Planning Commission of China, Guangzhou Science and	Some concerns

	Age (IQR) Intervention: 57 (51 – 64) Control: 58 (48 – 63) Sex (%, male) Intervention: 38% Control: 44% Histology: NSCLC	Patients had at least 3 BMs	chemotherapy (4–6 cycles, until unacceptable adverse events or intracranial disease progression occurred).			Technology Bureau, Betta Pharmaceuticals, and the Chinese Thoracic Oncology Group[4]	
Subquestion 2: Sequence of therapy							
No studies reported							
Subquestion 3: Systemic therapy for brain metastases from lung cancer, previously locally treated							
Study	**Participants**	**Inclusion criteria brain metastases**	**Comparison**	**Follow-up**	**Outcome measures**	**Comments**	**Risk of bias (per outcome measure)***
Yu, 2022	N at baseline Intervention: Control:	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: NR	Intervention: ALKis Control: Placebo, chemotherapy, another ALKis	Ranged from 8.6 months to 50.9 months	PFS OS	NA	

	Histology: Not specified to specific histology						
Zheng, 2023	N at baseline Intervention: Control: Histology: NSCLC	Presence of a driver mutation/translocation: ALK-TKI Symptomatic/asymptomatic brain metastases: NR	Intervention: ALKis Control: Placebo, chemotherapy, another ALKis	NA	PFS	Supported by the Basic Public Welfare Research Program of Zhejiang Province (LGF20G030004) [4]. The Natural Science Foundation of Zhejiang Provincial (LYQ20H310003)[4]	
Schuler, 2016 Lux-Lung 3 Lux-Lung 6	N at baseline Intervention: 35 Control: 46 Age (median, range) Lux-Lung 3 Intervention: 60.5 (37-71) Control: 53.5 (30-78) Lux-Lung 6 Intervention: 63.0 (71-74) Control: 55.0 (35-70)	Presence of a driver mutation/translocation: EGFR-TKI Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR	Intervention: Afatinib Control: 6 cycles of intravenous platinum-based chemotherapy Lux-Lung 3 Cisplatin (75 mg/m2) + Pemetrexed (500 mg/m2, once) Lux-Lung 6 Gemcitabine (1000 mg/m2, on days 1 and 8) + cisplatin (75 mg/m2, on day 1 of a 21-day cycle)	Mortality	PFS OS	Funded by Boehringer Ingelheim[4]	High

	Sex (%, male) Lux-Lung 3 Intervention: 30% Control: 35.7% Lux-Lung 6 Intervention: 20% Control: 55.0 33.3% Prior WBRT (%) Lux-Lung 3 Intervention: 35% Control: 33.3% Lux-Lung 6 Intervention: 21.4% Control: 33.3% Histology: NSCLC						
Reungwetwattan,2018	N at baseline Intervention: 61 Control: 67	Presence of a driver mutation/translocation: EGFR-TKI	Intervention: Osimertinib (80 mg once daily)	18 months, then every 12 weeks until systemic disease progression	CNS PFS	Funded by AstraZeneca[4]	Some concerns

	Age (range) Intervention: 63 (34-83) Control: 63 (39-85) Sex (%, male) Intervention: 38% Control: 39% Histology: NSCLC All patients had Adenocarcinoma	Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR Prior treatment for brain metastases (radiotherapy): Intervention: 24% Control: 25%	Control: Standard EGFR-TKIs (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily)				
Peters, 2017	N at baseline Intervention: 64 Control: 58 Age (mean, SD), not reported for CNS patients only. Intervention: 56.3 ± 12.0	Presence of a driver mutation/translocation: ALK-TKI Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR	Intervention: Alectinib (600 mg twice daily; to be taken with food) Control: Crizotinib (250 mg twice daily; to be taken with food)	The median duration of followup was 17.6 months (range, 0.3 to 27.0) in the crizotinib group and 18.6 months (range, 0.5 to 29.0) in the alectinib group.	PFS	Source of funding: Financial support from Hoffman-La Roche[4]	LOW

	Control: 53.8 ±13.5 Sex (%, male), not reported for CNS patients only. Intervention: 45% Control: 42% Prior treatment (%) Intervention: 40% Control: 38% Histology: NSCLC	Prior treatment for brain metastases (brain surgery, radiosurgery, WBRT, other): Intervention: 40% Control: 38%					
Soria, 2017	N at baseline Intervention: Control: Age (SD) Intervention: 189 Control: 187	Presence of a driver mutation/translocation: ALK-TKI Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR Brain metastases (%):	Intervention: Ceritinib (750 mg/day orally (given in a fasted state) daily) Control: Chemotherapy (cisplatin [75 mg/m²], or carboplatin [target area under the curve of 5–6] plus pemetrexed [500 mg/m²]) given every 21 days)	The median duration between randomisation and progression-free survival analysis for all patients was 19·7 months	PFS	Funded by Novartis Pharmaceuticals Corporation[4]	High

	Sex (%, male) Intervention: 46% Control: 39% Histology: NSCLC	Intervention: 31% Control: 33% Prior treatment for brain metastases: Intervention: 31% Control: 33%					
Solomon, 2016	N at baseline Intervention: 39 Control: 40 Age (median, range) Intervention: 48 (29-70) Control:51(25-76) Sex (%, male) Intervention: 51% Control: 23% More men in the intervention group	Presence of a driver mutation/translocation: ALK-TKI Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: no ongoing corticosteroid requirement Prior treatment for brain metastases	Intervention: Crizotinib (250 mg twice daily) Control: Chemotherapy (pemetrexed 500 mg/m2 plus either cisplatin 75 mg/m2 or carboplatin area under the curve of 5 to 6 mg$min/mL; all given every 3 weeks for a maximum of six cycles).	±31 weeks	PFS	Funded by Pfizer[4]	High

	Histology: NSCLC						
Shaw, 2017	N at baseline Intervention: 65 Control: 69 Age (median, range) Intervention: 54.0 (44.0-63.0) Control: 54.0 (47.0-64.0) Sex (%, men) Intervention: 41% Control:47 Histology: NSCLC	Presence of a driver mutation/translocation: ALK-TKI Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: no therapy within 2 weeks before study entry Prior treatment for brain metastases (radiotherapy): Intervention: 56% Control: 47%	Intervention: Ceritinib (orally, 75 mg per day, in continuous 21 dat treatment cycles) Control: Chemotherapy (intravenous pemetrexed 500 mg/m² or docetaxel 75 mg/m² [investigator choice], every 21 days)	Total group: Median follow-up (16·5 months [IQR 11·5–21·4]) was 16·6 months (11·6–21·4) for the ceritinib group and 16·4 months (11·4–21·4) for the chemotherapy group.	PFS	Funded by Novartis Pharmaceuticals Corporation[4]	
Camidge, 2018	N at baseline Intervention: 40 Control: 41	Presence of a driver mutation/translocation: ALK-TKI	Intervention: Brigatinib (orally, 180 mg once daily after a 7-day lead-in period of 90 mg once)	NR	PFS (CNS)	Funded by Ariad Pharmaceuticals[2]	High

	Age (median, range) Intervention: 58 (27–86) Control: 60 (29–89) Sex (%, male) I: 50% C: 61 % Histology: NSCLC	Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR Prior treatment for brain metastases (radiotherapy), total N: Intervention:18 Control: 19	Control: Crizotinib (250 mg twice daily)				
Edelman, 2010	N at baseline Intervention: 66 Control: Age (median, range) Intervention: 58 (27–86) Control: 60 (29–89)	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR Prior treatment for brain metastases with surgery or WBRT	Arm A: Gemcitabine (1000 mg/m2 infused over 30 min on days 1 and 8 plus carboplatin AUC 5.5 over 15–30 min on day 1 (GC)) Arm B: Gemcitabine (1000 mg/m2 infused over 30 min on days 1 and 8 plus paclitaxel 200 mg/m2 infused over 3 h on day 1 (GP)) Arm C: Paclitaxel (225 mg/m2 infused over 3 h on day 1 plus carboplatin AUC	Mortality	OS PFS	Conflict of interest[3]	Some concerns

	Sex (%, male) Intervention: 50% Control: 61 % Histology: NSCLC	Patients were stratified by presence of brain metastases	6.0 over 15–30 min on day 1 (PC))				
Liu, 2010	N at baseline Intervention: 20 Control: 19 Age (SD) Intervention: 56.7 ± 13.7 Control: 57.9 ± 13.8 Sex (%, male) Intervention: 65% Control: 68% Histology: SCLC	Not reported if there was prior treatment for brain metastases Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR % with more than 1 BM: Intervention: 35% Control: 53%		3 years	OS	NA	High
Subquestion 4: Systemic therapy with concurrent radiotherapy							

Lim, 2015	N at baseline: Intervention: Control: Age (SD) Intervention: Control: Sex (%, male) Intervention: Control: Histology: NSCLC	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR Prior treatment for brain metastases with surgery or WBRT Size brain metastases: max. diameter 3 cm	Intervention: SRS + Chemotherapy Control: Upfront chemotherapy	12 months	OS	Funded by Samsung Biomedical Research Institute Grant (SMX1132531) and by Elekta Korea research funds [1,4]	High
Lee, 2008	N at baseline: Intervention: Age (SD) Intervention: Control: Sex (%, male) Intervention:	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR	Intervention: Chemo + WBRT Control: WBRT + Chemo	Mortality, with a median follow-up of 40 months (range, 20-59)	OS PFS	Supported by grants NCC-0210140 and 0510140 from the National Cancer Center [1,4]	High

	Control: Histology: NSCLC						
Lee, 2014	N at baseline Intervention: 40 Control: 40 Age (median, range) Intervention: 61.3 (48-75) Control: 62.2 (41-73) Sex (%, male) Intervention: 38% Control: 21% Histology: NSCLC	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR Patients had not previously been treated for BM	Intervention: WBRT + erlotinib Control: WBRT + placebo	12.6 months	OS PFS	Funded by Cancer Research UK, University College London and University College London Hospital Comprehensive Biomedical Research Centre[1]	High
Quantin, 2010	N at baseline: Intervention:37 Control: 33	Absence of a driver mutation/translocation	Intervention: Cisplatin-vinorelbine-ifosfomide Control: ifosfamide	The minimal follow-up period was 21 months.	OS PFS	This study was supported by Essai Therapeutique Neo-Adjuvante (Montpellier) and Clinical Research Department	

	Age (SD) Intervention: 59.1 ± 7.8 Control: 56 ± 9.5 Sex (%, male) Intervention: 76% Control: 76% Histology: NSCLC	Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR				of the Montpellier Academic Hospital[4]	
Guerrieri, 2004	N at baseline: Intervention: 21 Control: 21 Age (range) Intervention: 63 (29-78) Control: 60 (42-77) Sex (%, male)	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR	Intervention: WBRT Control: WBRT + concomitant carboplatin	NR	OS	NA	High

	Intervention: 71% Control: 71% Histology: NSCLC						
Sperduto, 2013	N at baseline Arm 1: 44 Arm 2: 40 Arm 3: 41 Age (median) Arm 1: 64 Arm 2: 63 Arm 3: 61 Sex NR Histology: NSCLC	Absence of a driver mutation/translocation Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR Previous treatment with radiotherapy for BM was not allowed Number of BMs: 1 to 3 Size of BMs: maxium size of ≤ 4.0 cm	Intervention Arm 1: WBRT + SRS Arm 2: WBRT + SRS + TMZ Arm 3: WBRT + SRS + ETN Control: see intervention	NR	OS	"RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the National Cancer Institute (NCI)[1,4]	High
Pesce, 2012	N at baseline Intervention: 16	Absence of a driver mutation/translocation	Intervention: WBRT (standard cranial irradiation (6–10 MV photons) of 10 · 3 Gy, without cone down or	NR	OS	The trial was supported with free drug supply and an unrestricted	High

	Control: 43 Age (range) Intervention: 57 (48-82) Control: 63 (45-79) Sex (%, male) Intervention: 56% Control: 63% Histology: NSCLC	Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: stable or decreasing dose for at least 4 days	boost) + gefinitub (250 mg p.o. daily Continuously) Control: WBRT (standard cranial irradiation (6–10 MV photons) of 10 · 3 Gy, without cone down or boost) + temozolomide (75 mg/m2 p.o. daily · 21/28 days, starting on day 1 of RT and to be continued until disease progression or intolerance)			educational grant by Essex Chemie (subsidiary of Schering-Plough), Switzerland and AstraZeneca (Switzerland). It has also been funded by the Swiss State Secretariat for Education and Research (SER)[1,2]	
Chua, 2010	N at baseline Intervention: 47 Control: 48 Age (range) Intervention: 59 (38-78) Control: 62 (43-79)	Absence of a driver mutation/translocation Previous treatment with radiotherapy for BM was not allowed Symptomatic/asymptomatic brain metastases: NR	Intervention: WBRT (30 Gy in 10 fractions over 2 weeks) + Temozolomide Control: WBRT (30 Gy in 10 fractions over 2 weeks)	Mortality	OS	Funding for medical editorial assistance was provided by Schering- Plough Corporation[1]	Some concerns

	Sex (%, male) Intervention: 64% Control: 67% Histology: NSCLC	Corticosteroid use: NR Number of BMs: ≥1					
Liu, 2010	N at baseline Intervention: 20 Control: 19 Age (SD) Intervention: 56.7 ± 13.7 Control: 57.9 ± 13.8 Sex (%, male) Intervention: 65% Control: 68% Histology: SCLC	Previous treatment for BM was unclear Symptomatic/asymptomatic brain metastases: NR Corticosteroid use: NR More than 1 brain metastases (%) Intervention: 35% Control: 53%	Intervention: sequential WBRT (1.8–2 Gy/time for 18–20 times, and the total dose in four weeks was 36 Gy) + systemic chemotherapy (Vm26 60 mg/m2, from Day 1 to Day 3; DDP 20 mg/m2,, from Day 1 to Day 5. One circle was defined as a 21-day therapy duration, and totally 4 circles involved) Control: Parallel WBRT (1.8–2 Gy/time for 18–20 times, and the total dose in four weeks was 36 Gy) + systemic chemotherapy (Vm26 60 mg/m2, from Day 1 to Day 3; DDP 20 mg/m2,, from Day 1 to Day 5. One circle was defined as a 21-day therapy duration, and totally 4 circles involved)	3 years	OS	NR	High

Neuhaus, 2009	N at baseline Intervention:47 Control: 49 Age (median, range) Intervention: 58 (34-75) Control: 59 (42-75) Sex (%, male) Intervention: 68% Control: 61% Histology: Not specified to specific histology	Symptomatic/asymptomatic brain metastases: Asymptomatic Corticosteroid use: NR Previous treatment with radiotherapy for BM or resection was not allowed	Intervention: Topotecan + WBRT (30 min infusion with 0.4 mg m^{-2} day^{-1} for 5 days over 4 weeks within 2 h before radiation therapy. Whole Brain Radiation (WBR) was applied with a fraction size of 2Gy day^{-1} to a total of 40 Gy) Control: WBRT (fraction size of 2Gy day^{-1} to a total of 40 Gy)	NR	OS PFS	Funded by GlaxoSmithkline[4]	High

For further details, see risk of bias table in the appendix

[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.