Supplementary Materials

Clinical Management of Patients With Non-Small Cell Lung Cancer, Brain Metastases, and Actionable Genomic Alterations: A Systematic Literature Review

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Appendices

Table S1 Search strategy from larger project of any metastatic NSCLC

Original searches from larger project of any metastatic NSCLC – June 10, 2021

Database(s) searched: Embase; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

#	Concept -- Conditions	Search string	Results as of June 10, 2021
1	Non-small cell lung cancer - title/abstract	(((nonsmall or non-small or "non small") and (lung or pulmonar*)) or NSCLC).ab,ti.	203,800
2	Advanced/metastases-title/abstract	(metasta* or advanced or "stage III*" or "stage 3*" or "stage IV" or "stage 4" or unresectable or recurrent).ab,ti.	3,075,810
3	Actionable and non-actionable populations-title/abstract/MeSH/Emtree field search	(actionable or non-actionable or nonactionable or "non actionable" or PD-L1 or PDL1).ab,ti. or (mutation* or aberration or genomic or genetic* or profile* or profiling).ab,ti. or (EGFR or "epidermal growth factor receptor" or ALK or "anaplastic lymphoma kinase" or ROS1 or NTRK or "tyrosine receptor kinase" or BRAF or B-Raf or KRAS or NRAS or HER2 or HER3 or "Human Epidermal growth factor Receptor" or proto-oncogene or protooncogene or oncogene).ab,ti. or (egfr or "epidermal growth factor receptor" or egfr-m or egfrm or "egf receptor" or ErbB or EGFRwt or EGFR-wt).ab,ti.	6,007,263
4	COMBINE conditions	#1 AND #2 AND #3	39,852
#	**Concept -- Topic area/outcomes**	**Search string**	
5	Epidemiology, co-mutations-title/abstract/MeSH/Emtree field search	(incidence or prevalence or death or mortality or co-mutation* or comutation* or coexpression or overexpression).ab,ti,xs,sh.	7,437,232
6	Clinical management-title/abstract/MeSH/Emtree field search	(("health care" or healthcare or resource) adj ("use" or utilization or utilisation)).ab,ti. or (admission or readmission or re-admission or hospitali* or attrition).ab,ti,xs,sh. or ((manag* or treat*) and (adverse adj2 (event* or effect* or outcome*))).ab,ti. or (inpatient or in-patient or end-of-life or "end of life" or "standard of care").ab,ti.	2,585,094

7	Review of outcomes-title/abstract/MeSH/Emtree field search	((overall or progression-free or "progression free") and (survival)).ab,ti. or (PFS or " response rate" or ORR or "duration of response" or DoR or "duration of treatment" or DoT or "time to" or "time-to" or "clinical benefit response" or "clinical benefit rate" or CBR or "disease control rate" or DCR or PFS2).ab,ti. or (adverse* or safe* or discontinu* or harm or harms or fatal* or death*).ab,ti.	13,154,974
8	Treatment pathways-title/abstract/MeSH/Emtree field search	(guideline* or consensus or "clinical practice" or "practice pattern" or "practice patterns" or "treatment pattern" or "treatment patterns").ab,ti,xs,sh.	1,995,421
#	**Concept -- Study design**	**Search string**	
9	Clinical trial design string-title/abstract/MeSH/Emtree field search	(Randomized Controlled Trial).pt. or (Controlled Clinical Trial).pt. or (randomized or randomised or randomly).ab,ti.	2,893,882
10	RWE design string-title/abstract/MeSH/Emtree field search	(incidence or prevalence or epidemiology or 'epidemiological data' or 'epidemiologic studies').ab,ti. or (observational or prospective* or retrospective* or 'cohort study' or cross-sectional or 'cross sectional' or regist*).ab,ti. or ('population based' or 'real world' or 'real-world' or 'claims data' or 'claims review' or 'claims analysis').ab,ti,sh,xs.	8,596,249
11	COMBINE topic areas with Clinical trial designs	(#5 OR #6 OR #7) AND #9	1,513,564
12	COMBINE topic areas with RWE study designs	(#5 OR #6 OR #7) AND #10	6,053,896
13	COMBINE all topic areas and study design concepts	#8 OR #11 OR #12	8,423,762
#	**COMBINE Concepts**	**Search string**	
14	Conditions + topic areas	#4 AND #13	17,780
15	Conditions + topic areas + English	limit #14 to English	17,308
16	Conditions + topic areas + English + date limit	limit #15 to last 5 years	10,957
17	Remove duplicates between MEDLINE and Embase	#16 deduplicated	8,015

Updated searches from larger project of any metastatic NSCLC – September 7, 2022

Database(s) searched: Embase; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

#	Concept – Conditions	Search string	Results as of September 7, 2022
1	Non-small cell lung cancer - title/abstract	(((nonsmall or non-small or "non small") and (lung or pulmonar*)) or NSCLC).ab,ti.	229,018
2	Advanced/metastases - title/abstract	(metasta* or advanced or "stage III*" or "stage 3*" or "stage IV" or "stage 4" or unresectable or recurrent).ab,ti.	3,365,317
3	Actionable and non-actionable populations, including EGFRm - title/abstract/MeSH/Emtree field search	(actionable or non-actionable or nonactionable or "non actionable" or PD-L1 or PDL1).ab,ti. or (mutation* or aberration or genomic or genetic* or profile* or profiling).ab,ti. or (EGFR or "epidermal growth factor receptor" or ALK or "anaplastic lymphoma kinase" or ROS1 or NTRK or "tyrosine receptor kinase" or BRAF or B-Raf or KRAS or NRAS or HER2 or HER3 or "Human Epidermal growth factor Receptor" or proto-oncogene or protooncogene or oncogene).ab,ti. or (egfr or "epidermal growth factor receptor" or egfr-m or egfrm or "egf receptor" or ErbB or EGFRwt or EGFR-wt).ab,ti.	6,540,932
4	COMBINE conditions	#1 AND #2 AND #3	47,305
#	**Concept -- Topic area/outcomes**	**Search string**	
5	Epidemiology, co-mutations - title/abstract/MeSH/Emtree field search	(incidence or prevalence or death or mortality or co-mutation* or comutation* or coexpression or overexpression).ab,ti,xs,sh.	8,139,996
6	Clinical management - title/abstract/MeSH/Emtree field search	(("health care" or healthcare or resource) adj ("use" or utilization or utilisation)).ab,ti. or (admission or readmission or re-admission or hospitali* or attrition).ab,ti,xs,sh. or ((manag* or treat*) and (adverse adj2 (event* or effect* or outcome*))).ab,ti. or (inpatient or in-patient or end-of-life or "end of life" or "standard of care").ab,ti.	2,909,321

7	Review of outcomes - title/abstract/MeSH/Emtree field search	((overall or progression-free or "progression free") and (survival)).ab,ti. or (PFS or "response rate" or ORR or "duration of response" or DoR or "duration of treatment" or DoT or "time to" or "time-to" or "clinical benefit response" or "clinical benefit rate" or CBR or "disease control rate" or DCR or PFS2).ab,ti. or (adverse* or safe* or discontinu* or harm or harms or fatal* or death*).ab,ti.	14,404,820
8	Treatment pathways - title/abstract/MeSH/Emtree field search	(guideline* or consensus or "clinical practice" or "practice pattern" or "practice patterns" or "treatment pattern" or "treatment patterns").ab,ti,xs,sh.	2,221,073
#	**Concept -- Study design**	**Search string**	
9	Clinical trial design string - title/abstract/MeSH/Emtree field search	(Randomized Controlled Trial).pt. or (Clinical Trial).pt. or (randomized or randomised or randomly).ab,ti. or (trial).ti.	3,129,907
10	RWE design string - title/abstract/MeSH/Emtree field search	(incidence or prevalence or epidemiology or 'epidemiological data' or 'epidemiologic studies').ab,ti. or (observational or prospective* or retrospective* or 'cohort study' or cross-sectional or 'cross sectional' or regist*).ab,ti. or ('population based' or 'real world' or 'real-world' or 'claims data' or 'claims review' or 'claims analysis').ab,ti.	9,566,921
11	COMBINE topic areas with Clinical trial designs	(#5 OR #6 OR #7) AND #9	1,653,650
12	COMBINE topic areas with RWE study designs	(#5 OR #6 OR #7) AND #10	6,737,154
13	COMBINE all topic areas and study design concepts	#8 OR #11 OR #12	9,332,054
#	**COMBINE Concepts**	**Search string**	
14	Conditions + topic areas	#4 AND #13	21,669
15	Conditions + topic areas + English	limit #14 to English	21,146
16	Conditions + topic areas + English + date limit	limit #15 to time since last search (2021–current)	4924
17	Exclude conference abstracts	16 not “conference abstract”.pt. MEDLINE = 1624 Embase = 1596	3220

18	Remove duplicates between MEDLINE and Embase	#17 deduplicated	1756

Table S2 Search strategy specific to brain metastases in NSCLC.

Original searches specific to brain metastases in NSCLC – June 17, 2021

Database(s) searched using the OvidSP platform: EBM Reviews-Cochrane Central Register of Controlled Trials, Embase, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

#	Concept -- Conditions	Search string	Results as of June 17, 2021
1	Non-small cell lung cancer-title/abstract	(((nonsmall or non-small or "non small") and (lung or pulmonar*)) or NSCLC).ti,ab	218,555
2	Brain metastases-title/abstract/MeSH/Emtree field search	"brain neoplasms"/ or "brain tumor"/ or (brain or cerebr* or "central nervous system" or CNS).ti,ab,kf	3,645,351
3	COMBINE conditions	#1 AND #2	13,870
#	**Concept -- Topic area/outcomes**	**Search string**	**Results**
4	Clinical characteristics: Natural history/disease symptoms/pathology-title/abstract/MeSH/Emtree field search	("natural history" or "disease burden" or "burden of disease" or incidence or prevalence or signs or symptoms or death or mortality or pathology*).ab,ti. or exp disease progression/	9,971,934
5	Clinical management: Standard of care-title/abstract/MeSH/Emtree field search	("standard of care" or "standard care" or guideline* or consensus or "clinical practice" or "practice pattern" or "practice patterns" or "treatment pattern" or "treatment patterns").ti,ab,xs,sh.	2,213,523
6	Unmet need: Unmet needs/outcomes-title/abstract/MeSH/Emtree field search	("unmet need" or "unmet needs" or "needs assessment" or response or responses).ab,ti. or exp treatment response/ or exp treatment response time/	6,718,634

7	Emerging therapies: Therapies-title/abstract	((emerging or new or novel) and (therap* or treatment*)).ti,ab or (ADC or antibody-drug conjugate* or monoclonal antibod* or immunotherap* or small molecule inhibitor* or tyrosine kinase inhibitor* or TKI*).ti,ab	3,593,298
8	COMBINE topics/outcomes	#4 OR #5 OR #6 OR #7	19,139,621
#	**COMBINE Concepts**	**Search string**	**Results**
9	Conditions + topic areas	#3 AND #8	10,307
10	Conditions + topic areas + English	limit #9 to English	9609
11	Conditions + topic areas + English + date limit	limit #10 to last 5 years	5937
13	Conditions + topic areas + English + date limit	Remove duplicates between MEDLINE, Embase, and Cochrane	4136

Updated searches specific to brain metastases in NSCLC – September 26, 2022

Database(s) searched: Embase; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

#	Concept -- Conditions	Search string	Results as of September 26, 2022
1	Non-small cell lung cancer - title/abstract	(((nonsmall or non-small or "non small") and (lung or pulmonar*)) or NSCLC).ti,ab	246,407
2	Brain metastases - title/abstract/MeSH/Emtree field search	"brain neoplasms"/ or "brain tumor"/ or (brain or cerebr* or "central nervous system" or CNS).ti,ab,kf	3,954,198
3	COMBINE conditions	#1 AND #2	16,461
#	**Concept -- Topic area/outcomes**	**Search string**	**Results**
4	Clinical characteristics: Natural history/disease symptoms/pathology - title/abstract/MeSH/Emtree field search	("natural history" or "disease burden" or "burden of disease" or incidence or prevalence or signs or symptoms or death or mortality or pathology*).ab,ti. or exp disease progression/	10,923,477

5	Clinical management: Standard of care - title/abstract/MeSH/Emtree field search	("standard of care" or "standard care" or guideline* or consensus or "clinical practice" or "practice pattern" or "practice patterns" or "treatment pattern" or "treatment patterns").ti,ab,xs,sh.	2,478,469
6	Unmet need: Unmet needs/outcomes - title/abstract/MeSH/Emtree field search	("unmet need" or "unmet needs" or "needs assessment" or response or responses).ab,ti. or exp treatment response/ or exp treatment response time/	7,262,003
7	Emerging therapies: Therapies - title/abstract	((emerging or new or novel) and (therap* or treatment*)).ti,ab or (ADC or antibody-drug conjugate* or monoclonal antibod* or immunotherap* or small molecule inhibitor* or tyrosine kinase inhibitor* or TKI*).ti,ab	3,984,154
8	COMBINE topics/outcomes	#4 OR #5 OR #6 OR #7	20,867,775
#	**COMBINE Concepts**	**Search string**	**Results**
9	Conditions + topic areas	#3 AND #8	12,494
10	Conditions + topic areas + English	limit #9 to English	11,999
11	Conditions + topic areas + English + date limit	limit #10 to 2021–current Medline = 768 Embase = 1742 Cochrane = 165	2675
12	Conditions + topic areas + English + date limit	Remove duplicates between MEDLINE, Embase, and Cochrane	1862

Fig. S1 Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2) summary of studies in AGA subgroup analysis

+ = low risk, ! = some concerns, - = high risk
D1 = Randomisation process, D2 = Deviations from the intended interventions, D3 = Missing outcome data, D4 = Measurement of the outcome, D5 = Selection of the reported result

Fig. S1 Legend: Figure S1 uses the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2) to summarize the studies in the actionable genomic alterations subgroup analysis. Most studies were deemed low risk in the various categories including randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Table S3 Other metastases reported and progression-free survival (PFS) for subgroup of patients with NSCLC, brain metastases, and actionable genomic alterations

Author Year	Line of therapy	Treatment	Other metastases reported	PFS, median, months
Addeo et al. 2021 [17]	1L	1G or 2G EGFR TKI	–	–
Bai et al. 2017 [18]	2L	GEF	Y	11.3
		ERL		10.8
Baldacci et al. 2022 [19]	2L+	LOR	–	–
Bilgin et al. 2021 [20]	1L	AFA	–	13.4
		ERL or GEF	–	11.6
Bozorgmehr et al. 2021 [21]	1L to > 3L	EGFR TKI, CT, palliative RT, de novo stage IV	–	–
		EGFR TKI, CT, palliative RT, secondary stage IV	–	–
Camidge et al. 2018 [22]	1L	Brigatinib	Y	24
		CRIZ	–	5.5
Chang et al. 2021 [23]	1L	EGFR TKI (GEF, ERL, AFA)	–	12.2
Chen et al. 2020 [24]	1L to 2L	EGFR TKI only	Y	–
		EGFR TKI + WBRT	Y	–
Chen et al. 2019a [25]	1L	GEF	Y	12.1
		ERL	Y	10.6
		AFA	Y	10.4
Chen et al. 2019b [26]	1L+	EGFR TKI + WBRT	–	–
		EGFR TKI alone		
Chen et al. 2018 [27]	1L or 2L	EGFR TKIs alone	–	7.8
		EGFR TKIs + concurrent WBRT		9.4
		WBRT followed by EGFR TKIs		8.3
Chiu et al. 2022 [28]	1L	EGFR TKI (GEF or ERL) ± BEV	–	–
de Marinis et al. 2021 [29]	1L+	AFA	–	10.1
Doherty et al. 2017 [30]	1L	WBRT + SRS + TKIs	Y	–
		SRS + TKIs	Y	
		TKIs	Y	
Duruisseaux et al. 2017 [31]	1L+	CRIZ	–	–
El Shafie et al. 2021 [32]	1L+	Delayed local therapy	–	–
		Early local therapy	–	–
Gijtenbeek et al. 2020 [33]	1L	ERL	–	–
		GEF		
		AFA		
He et al. 2019 [34]	1L	EGFR TKI (GEF, ERL, ICO) + WBRT	Y	–
		EGFR TKI (GEF, ERL, ICO)	Y	–
Horn et al. 2021 [35]	1L	Ensartinib	–	11.8
		CRIZ	–	7.5
Huang et al. 2021 [36]	1L+	GEF/ERL	–	–
		AFA		
Huang et al. 2022 [37]	1L	AFA	–	–
Hyun et al. 2020 [38]	–	EGFR TKI (GEF, ERL, AFA)	Y	11.6
		WBRT followed by EGFR TKI (GEF, ERL, AFA)	Y	10.6
		SRS followed by EGFR TKI (GEF, ERL, AFA)	Y	–
Ito et al. 2021 [39]	1L	AFA	–	–
		OSI		
Jahanzeb et al. 2020 [40]	1L and 2L	ALK TKIs (CRIZ, CER, ALEC, BRIG)	–	4.9
Jia et al. 2019 [41]	1L	SRS + EGFR TKI (GEF, ERL)	Y	10.7
		WBRT + EGFR TKI (GEF, ERL)	Y	9.8
Jiang et al. 2019 [42]	1L	EGFR TKI (GEF, ERL, ICO) + BEV	Y	14.4
		EGFR TKI (GEF, ERL, ICO)	Y	9
Jung et al. 2020 [43]	1L	GEF	–	–
		ERL	–	–
		AFA	–	–
Jung et al. 2022 [44]	1L and 2L	1L AFA + 2L OSI	–	–
		1L AFA + 2L CT or other treatments		
		1L AFA + 2L systemic treatment or SC		
		1L AFA only		
Ko et al. 2022 [45]	1L	GEF or ERL or AFA ± denosumab	–	–
Kong et al. 2021 [46]	–	EGFR TKI (AFA, ERL, GEF)	–	–
Lee et al. 2021 [47]	1L to 2L	AFA	–	–
Lee et al. 2019a [48]	1L+	EGFR TKI + brain surgery + WBRT	Y	–
		EGFR TKI + WBRT	Y	–

Lee et al. 2019b [49]	–	WBRT	Y	6.9
		SRS	Y	14
		Delayed radiation	Y	7.9
		Never cranial irradiation	Y	8.5
Lee et al. 2020 [50]	–	With or without OSI	–	–
Li et al. 2017 [51]	–	EGFR TKI (GEF or ERL) or EGFR TKI (GEF or ERL) + WBRT	–	–
Li et al. 2019 [52]	1L	WBRT followed by EGFR TKI (GEF, ERL, ICO)	Y	–
		EGFR TKI (GEF, ERL, ICO) + WBRT	Y	–
		EGFR TKI (GEF, ERL, ICO) followed by WBRT	Y	–
Lin et al. 2019 [53]	1L	GEF	Y	8
		ERL	Y	13
		AFA	Y	11
Liu et al. 2017 [54]	1L to 2L	EGFR TKI (GEF, ERL, ICO) + early RT (WBRT, SRS)	–	–
		EGFR TKI (GEF, ERL, ICO)	–	–
		EGFR TKI (GEF, ERL, ICO) + salvage RT (WBRT, SRS)	–	–
Liu et al. 2020 [55]	1L to > 4L	OSI	–	9.1
		OSI + ASA	–	21.3
Lu et al. 2022a [56]	1L	Aumolertinib	–	15.3
		GEF	–	8.2
Lu et al. 2022b [57]	2L and 3L	Sintilimab + IBI305 + CT	–	7.2
		Sintilimab + CT	–	–
		CT alone	–	4.3
Magnuson et al. 2017 [58]	1L	ERL followed by WBRT or SRS	Y	–
		WBRT followed by ERL	Y	–
		SRS followed by ERL	Y	–
Masuda et al. 2018 [59]	1L+	ALEC	–	–
Mehlman et al. 2019 [60]	1L and > 2L	OSI (≥2L with T790M)	–	–
		OSI (≥2L without T790M)		
		OSI (1L)		
Miyawaki et al. 2019 [61]	1L	EGFR TKI	Y	8.3
		Local therapy	Y	9
Mok et al. 2017 [62] Wu 2017 [63]	2L	OSI	–	8.5
		PBC + PEM		4.2
		OSI		–
		PBC + PEM		
Nadler et al. 2020 [64]	1L+	ERL	–	NR
Patel et al. 2017 [65]	1L+	ERL	–	12
Peters et al. 2017 [66]	1L	ALEC	–	25.4
		CRIZ	–	7.4
Ramotar et al. 2020 [67]	1L	SRS	Y	–
		WBRT	Y	
		TKI	Y	
Saida et al. 2019 [68]	1L	EGFR TKI without upfront brain RT	Y	–
		EGFR TKI with upfront brain RT	Y	–
Saito et al. 2019 [69]	1L	ERL + BEV	–	12.7
		ERL	–	11.2
Shaw et al. 2017 [70]	2L/2L+	CER	–	4.4
		CT	–	1.5
Shaw et al. 2020 [71]	1L	LOR	–	NR
		CRIZ	–	7.2
Shi et al. 2017 [72]	1L	ICO	–	–
		CT	–	–
Shi et al. 2022 [73]	1L	Furmonertinib	–	18
		GEF	–	11.2
Solomon et al. 2018 [74]	1L	CRIZ	–	–
		CT	–	–
Soria et al. 2017 [75]	1L	CER	–	10.7
		PBC	–	6.7
Soria et al. 2018 [76] Reungwetwattana et al. 2018 [77]	1L	OSI	–	NR
		GEF or ERL	–	13.9
Tang et al. 2021 [78]	–	OSI	–	–
Teocharoen et al. 2021 [79]	1L to > 2L	EGFR TKI	–	–
Tu et al. 2022 [80]	1L to 3L+	AFA	–	10.1
Wang et al. 2018 [81]	1L to > 2L	Asymptomatic pts EGFR TKI ± RT (WBRT, SRS)	Y	–
		Symptomatic pts EGFR TKI ± RT (WBRT, SRS)	Y	
Wang et al. 2020 [82]	–	None		
		RT (WBRT, SRS)		
		EGFR TKIs in TKI-naïve		
		CT		
		EGFR TKIs + RT (WBRT, SRS)		
Wolf et al. 2022 [83]	3L	ALEC	–	9.7

		PEM or DOC	–	1.4
Wu et al. 2018 [84]	1L	CRIZ	–	–
		CT	–	–
Yang et al. 2017a [85]	–	BEV + GEF + WBRT	–	–
		WBRT		
Yang et al. 2017b [86]	1L to 2L	ICO	Y	6.8
		WBRT ± CT	Y	3.4
Yang et al. 2021a [87]	2L	OSI	Y	4.5
		AFA	Y	3.9
Yang et al. 2021b [88]	–	Delayed RT	Y	–
		Upfront RT	Y	–
Yomo et al. 2018 [89]	1L+	SRS ± EGFR TKI (GEF, ERL, AFA, OSI)	Y	–
Yu et al. 2019 [90]	1L+	EGFR TKIs (ICO, GEF, ERL)	Y	–
Yu et al. 2021a [91]	1L to 2L	OSI with upfront cranial RT	Y	12.9
		OSI without upfront cranial RT	Y	11.3
Yu et al. 2021b [92]	1L to > 2L	EGFR TKI (GEF, ICO, ERL, AFA, OSI), local brain therapies (surgery, WBRT, SRS)	Y	–
Zeng et al. 2022 [93]	1L	EGFR TKI	–	13.7
Zhao et al. 2021 [94]	1L	APA + GEF	–	–
		PBO + GEF	–	
Zhao et al. 2019 [95]	2L+	WBRT (TKI-naïve group)	Y	–
		WBRT (TKI-resistant group)	Y	–
Zhao et al. 2022 [96]	1L	1G EGFR TKI (GEF or ERL)	–	13.7
		OSI	–	(all pts)
Zhou et al. 2019 [97]	1L	ALEC	–	NE
		CRIZ	–	9.2
Zhu et al. 2017 [98]	–	1G EGFR TKI + RT	Y	–
		1G EGFR TKI	Y	–

Dash (–) not reported; *1L/2L/3L/4L* first-/second-/third-/fourth-line, *1G/2G* first-/second-generation, *AFA* afatinib, *ALEC* alectinib, *ALK* anaplastic lymphoma kinase, *APA* apatinib, *B/C* before or concurrent, *BEV* bevacizumab, *BRIG* brigatinib, *CER* ceritinib, *CRIZ* crizotinib, *CT* chemotherapy, *DOC* docetaxel, *EGFR* epidermal growth factor receptor, *ERL* erlotinib, *GEF* gefitinib, *ICO* icotinib, *LOR* lorlatinib, *NE* not evaluable, *NR* not reached, *OSI* osimertinib, *PBC* platinum-based chemotherapy, *PBO* placebo, *PEM* pemetrexed, *PFS* progression-free survival, *pts* patients, *RT* radiotherapy, *SC* supportive care, *SRS* stereotactic radiosurgery, *TKI* tyrosine kinase

Table S4 Newcastle-Ottawa Scale (NOS) assessment for observational comparative studies in actionable genomic alteration subgroup analysis

Cohort studies	Selection				Comparability	Outcome			NOS Score
Author and year[a]	S1	S2	S3	S4	C5	O6	O7	O8	Total stars (max 9 stars)
Bilgin 2021	*	*	*	*	*	*	*		7
Bozorgmehr 2021	*	*	*	*	*	*	*		7
Chen 2018	*	*	*	*	*	*	*	*	8
Chen 2019	*	*	*	*	*	*	*	*	8
Chen 2020	*	*	*	*	*	*	*		7
Chiu 2022	*	*	*	*		*	*		6
Doherty 2017	*	*	*	*		*	*		6
El Shafie 2021	*	*	*	*	*	*	*		7
He 2019	*	*	*	*	*	*	*	*	8
Ito 2021	*	*	*	*		*	*		6
Jahanzeb 2020	*	*	*	*		*	*		6
Jiang 2019	*	*	*	*	*	*	*	*	8
Jung 2020	*	*	*	*		*	*		6
Ko 2022	*	*	*	*	*	*	*	*	8
Kong 2021	*	*	*		*				4
Lee 2019	*	*	*	*	*	*	*		7
Lee 2019	*	*	*	*	*	*	*	*	8
Li 2019	*	*	*	*	*	*	*		7
Lin 2019	*	*	*	*		*	*	*	7
Liu 2017	*	*	*	*	*	*	*	*	8
Liu 2020	*	*	*	*	*	*	*	*	8
Miyawaki 2019	*	*	*	*	*	*	*	*	8
Mehlman 2019	*		*	*	*	*			5
Nadler 2020	*	*	*	*	*	*	*		7
Patel 2017	*	*	*	*	*	*	*		7
Ramotar 2020	*	*	*	*		*	*		6
Teocharoen 2021	*	*	*	*	*	*	*		7
Yang 2017	*	*	*	*	*	*	*		7
Yang 2021	*	*	*	*	*	*	*		7
Yu 2021	*	*	*	*	*	*	*	*	8
Zeng 2022	*	*		*		*	*	*	6
Zhao 2019	*	*	*	*	*	*	*	*	8
Zhao 2022	*	*	*	*		*	*	*	7
Zhu 2017	*	*	*	*	*	*	*	*	8

NOS domains assessed; max of 9 stars for comparative studies:

S1: Representativeness of the exposed cohort; S2: Selection of the non-exposed cohort; S3: Ascertainment of exposure; S4: Demonstration that outcome of interest was not present at start of study; C5: Comparability of cohorts on the basis of the design or analysis (may be awarded up to 2 stars); O6: Assessment of outcome; O7: Was follow-up long enough for outcomes to occur; O8: Adequacy of follow up of cohorts.

Table S5 Newcastle-Ottawa Scale (NOS) assessment for non-comparative studies in actionable genomic alteration subgroup analysis

Cohort studies	Selection			Outcome			NOS Score
Author and year[a]	S1	S3	S4	O6	O7	O8	Total stars (max 6)
Addeo 2021	*	*	*	*	*	*	6
Bai 2017	*	*	*	*	*		5
Baldacci 2022	*	*	*	*	*	*	6
Chang 2021	*	*	*	*	*	*	6
Chen 2019	*	*	*	*	*		5
de Marinis 2021	*	*	*	*	*		5
Duruisseaux 2017	*	*	*	*	*	*	6
Gijtenbeek 2020	*	*	*	*	*		5
He 2021	*	*	*	*	*	*	6
Huang 2021	*	*	*	*	*		5
Huang 2022	*	*	*	*	*		5
Hyun 2020	*	*	*	*	*		5
Jung 2022	*	*	*	*	*		5
Lee 2020	*	*	*	*	*		5
Lee 2021	*	*	*	*	*		5
Li 2017	*	*	*	*	*	*	6
Magnuson 2017	*	*	*	*	*		5
Masuda 2018	*	*	*	*	*	*	6
Tang 2022	*	*	*	*	*		5
Tu 2022	*	*	*	*	*	*	6
Wang 2018	*	*	*	*	*	*	6
Wang 2020	*	*	*	*	*		5
Yang 2018	*	*	*	*	*	*	6
Yang 2021	*		*	*	*	*	5
Yomo 2018	*	*	*	*	*	*	6
Yu 2019	*	*	*	*	*		5
Yu 2021	*	*	*	*	*	*	6

NOS domains assessed; max of 6 stars for non-comparative studies:
S1: Representativeness of the exposed cohort; S3: Ascertainment of exposure; S4: Demonstration that outcome of interest was not present at start of study; O6: Assessment of outcome; O7: Was follow-up long enough for outcomes to occur; O8: Adequacy of follow up of cohorts.

Conference Abstracts

Although conference abstracts were not eligible for inclusion in the SLR, the most recent meetings of the following conferences were searched to provide a current view of the evidence landscape (Table S5). Among six conferences searched from the past two years, 56 abstracts were identified as being relevant to brain metastases in the NSCLC setting. Most of the conference abstracts focused on actionable populations, specifically *EGFR* mutations. Specific therapies evaluated in studies of *EGFR* included osimertinib (Chen et al.; Lorenzi et al.; de Mello Morais Mata, et al.), afatinib (Lee, et al.), aumolertinib (AENAS, Lu et al.), furmonertinib (FURLONG, Chen, et al.), neratinib (Goldman et al.), D-0316 (InventisBio, Lu et al.), EGFR TKIs

plus bevacizumab (Qin et al.; Wang et al.) and gefitinib plus chemotherapy (GAP Brain, Chen et al.). One study showed that osimertinib performed better than erlotinib or gefitinib; however, these results may have been due to treatment selection bias (Tatineni, et al.). Authors of all studies reported positive CNS efficacy or response.

Four other mutations were reported: *ALK, ROS1, KRAS*, and *MET*. Two studies evaluated alectinib for patients with *ALK* mutations (Krebs et al.; Zou et al.). Krebs et al. reported that outcomes were improved with first-line alectinib versus crizotinib. In the ALTA-1L trial, Tiseo et al. reported that brigatinib demonstrated durable overall and intracranial efficacy with manageable tolerability when compared with crizotinib in patients with treatment-naive *ALK*-positive NSCLC. Based on long-term data from the CROWN trial, Solomon et al. reported favorable efficacy of lorlatinib versus crizotinib in patients with treatment-naive *ALK*-positive NSCLC. A study of ROS1-positive mNSCLC suggested that crizotinib may be effective and well-tolerated (Dogen et al.). One study evaluated sotorasib for patients with *KRAS* G12C-mutated NSCLC with stable brain metastases (Ramalingam et al.). In another study, Swart et al. evaluated brain metastases in patients with *KRAS* G12C-mutated NSCLC and found that intracranial progression was more frequent in patients with baseline brain metastases and that the presence of baseline brain metastases did not influence survival for patients with (pretreated) *KRAS* G12C–mutated stage IV NSCLC treated with first-line (chemo)-immune checkpoint inhibitors. *MET* exon 14 skipping was evaluated in two studies (Ryder et al.; Scherz et al.); Scherz et al. evaluated tepotinib.

Studies of therapies targeting PD-1/PDL-1 were also identified. Favorable results were reported for first-line cemiplimab monotherapy compared with chemotherapy (Ozguroglu, et al.), pembrolizumab (Khurram Khan et al.), sintilimab plus docetaxel (Wang et al.), and atezolizumab in the prior-treated NSCLC setting (Ardizzoni et al.). Other therapies reported included temozolomide for patients with negative driving genes (Fan et al.) and the anti-vascular endothelial growth factor (VEGF) agents anlotinib (Zhu et al.) and apatinib (Han et al.; Zhang et al.).

In a study by Rakshit et al., the authors concluded that although patients with NSCLC with driver mutations had high incidence of brain metastases at diagnosis, these patients had more favorable outcomes than historical controls. The rationale in the difference was thought to be the availability potent active targeted therapies with good CNS penetration for patients with actionable mutations. Another study of overall survival suggested poor prognosis in patients with *KRAS* wildtype and *STK11* mutant or *KRAS* G12C co-occurring with *KEAP1* mutant, suggesting unmet needs in patients with STK11/KEAP1 mutations (Julian, et al.). A systematic review concluded that TKI alone resulted in superior results compared with TKI plus radiotherapy in patients with NSCLC and brain metastases (Tancherla et al.).

Among four studies that included patients without actionable mutations or targets, two were ongoing at the time of publication. One study compared Dato-DXd with docetaxel (Yoh et al.), and the other evaluated 4-demethyl-4-cholesteryloxycarbonyl-penclomedine (Weiner et al.). The other two studies included patients without *EGFR* or *ALK* genetic alterations and reported favorable results with atezolizumab plus carboplatin and pemetrexed (Nadal et al.) and first-line nivolumab plus ipilimumab combined with chemotherapy (Carbone et al.).

Table S6 Conferences and Abstract List

European Lung Cancer Congress (ELCC), March 25-27, 2021 = 13 abstracts	
Abstract # First author	**Title**
142P Tancherla et al.	EGFR-TKI plus Radiotherapy versus EGFR-TKI Only in Non-Small Cell Lung Cancer Patients with Brain Metastasis: A Systematic Review and Meta-Analysis of Observational Studies
156P Dogan et al.	Outcomes of ROS1 Positive Metastatic Lung Cancer Patients Treated with Crizotinib
38P Rakshit et al.	Brain metastases in non-small cell lung cancer in era of molecularly driven therapy
193P Kim et al.	Long-term survival in non-small cell lung cancer patients with metachronous brain-only oligorecurrence who underwent definitive treatment
192TiP Rebuzzi et al.	Radiological morphological (MF) and radiomic features (RF) of brain metastases in oncogene-addicted advanced non-small cell lung cancer (NSCLC) patients: diagnostic implications and prognostic role (BRAIN Lung study).
109P Perol et al.	Real-world evaluation of Pembrolizumab monotherapy for PD-L1 positive (TPS>50%) metastatic NSCLC in France
154P Zou et al.	Intracranial efficacy of Alectinib in ALK-positive NSCLC patients with CNS metastases--A multicenter retrospective study

European Lung Cancer Congress (ELCC), March 25-27, 2021 = 13 abstracts	
Abstract # First author	**Title**
180P Cui et al.	Incidence of brain metastases (BM) in newly diagnosed stage 4 NSCLC during COVID-19
151P Chen et al.	Osimertinib versus Standard-of-care EGFR-TKI as First-line Treatment for Advanced NSCLC with EGFR-positive Mutation Patients: A Systematic Review
149P Lorenzi et al.	First line (1L) osimertinib in EGFR mutant (mut) advanced non-small-cell lung cancer (aNSCLC) patients (pts): progression (PD) pattern and safety in the real-world (RW)
160P Ryder et al.	Non-interventional cohort study on patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring MET exon 14 (METex14) skipping in the US
157P Scherz et al.	Tepotinib in patients (pts) with MET exon 14 (METex14) skipping NSCLC: Efficacy results from all pts enrolled in VISION Cohort A
145P Miura et al.	UpSwinG: real-world, non-interventional cohort study on TKI activity in patients (pts) with EGFR mutation-positive (EGFRm+) NSCLC with uncommon mutations

European Lung Cancer Congress (ELCC), March 30-April 2, 2022 = 2 abstracts	
Abstract # First author	**Title**
29P Tiseo et al.	Brigatinib (BRG) vs crizotinib (CRZ) in anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor-naive ALK+ non-small cell lung cancer (NSCLC): ALTA-1L final results
9P Ardizzoni et al.	Final results from TAIL: Updated long-term safety and efficacy of atezolizumab (atezo) in a diverse population of patients (pts) with previously treated advanced NSCLC

American Association for Cancer Research (AACR), April 9-14, 2021 = 4 abstracts	
Abstract # First author	**Title**
CT152 Weiner et al.	Phase II clinical trial results for 4-demethyl-4-cholesteryloxycarbonyl-penclomedine (DM-CHOC-PEN) in advanced non-small cell lung cancer (NSCLC) involving the CNS
660 Julian et al.	Real-world prevalence of metastasis and overall survival (OS) in patients with advanced non-small cell lung cancer (aNSCLC) with KRAS G12C and with or without STK11 or KEAP1 mutations
2217 Xu et al.	More somatic mutations can be detected in cerebrospinal fluid ctDNA of NSCLC patients with brain metastases
CT170 (Lu et al.)	D-0316 in patients with advanced T790M-positive EGFR-mutant non-small cell lung cancer who progressed on prior EGFR-TKI therapy: results from a phase II study (NCT03861156)

American Association for Cancer Research (AACR), April 8-13, 2022 = 1 abstract	
Abstract # First author	**Title**
CT223 Solomon et al.	Updated efficacy and safety from the phase 3 CROWN study of first-line lorlatinib vs crizotinib in advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)

American Society of Clinical Oncology (ASCO), June 4-8, 2021 = 17 abstracts	
Abstract # First author	**Title**
9086 Janzic et al.	Real-world outcomes and clinical characteristics of patients with brain metastases from EGFR mutated non-small cell lung cancer: Data from a large retrospective study (REFLECT)
2033 Kawahara et al.	Presentation and management of patients with brain metastases of primary melanoma, non-small cell lung cancer, and breast cancer origin

American Society of Clinical Oncology (ASCO), June 4-8, 2021 = 17 abstracts	
Abstract # First author	**Title**
e21181 Dong et al.	Longitudinal sequencing of TCR and circulating tumor DNA revealing radiotherapeutic efficacy and prognosis for non-small cell lung cancer patients with brain metastasis.
e21028 Rauf et al.	Outcomes of KRAS mutated, EGFR mutated, ALK mutated and wildtype patients in non-small cell lung cancer brain metastases.
2034 Tatineni et al.	Outcomes of first, second, and third-generation anaplastic lymphoma kinase (ALK) inhibitors in non-small cell lung cancer brain metastases (NSCLCBM).
TPS9127 Yoh et al.	A randomized, phase 3 study of datopotamab deruxtecan (Dato-DXd; DS-1062) versus docetaxel in previously treated advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations (TROPION-Lung01).
2031 Tatineni et al.	Outcomes of first-generation versus third-generation epidermal growth factor receptor (EGFR) inhibitors in non-small cell lung cancer with brain metastases (NSCLCBM).
9085 Ozguroglu et al.	Cemiplimab monotherapy as first-line (1L) treatment of patients with brain metastases from advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥ 50%: EMPOWER-Lung 1 subgroup analysis.
2023 Wong et al.	A phase II trial combining nivolumab and stereotactic brain radiosurgery for treatment of brain metastases in patients with NSCLC.
e21063 Zhuet al.	A phase II study of anlotinib plus whole brain radiation therapy (WBRT) for advanced non-small cell lung cancer with multiple brain metastases.
e21216 de Mello Morais Mata et al.	Overall survival comparison in patients with and without brain metastases treated with osimertinib for metastatic EGFR mutation positive non-small cell lung cancer (NSCLC).
2028 Wang et al.	The efficacy and clinical survival outcome of different first-line treatments in EGFR-mutant non-small cell lung cancer with brain metastases.
9114 Gerardo Arrieta Rodriguez et al.	Nitroglycerin (NTG) plus whole intracranial radiotherapy for brain metastases (BM) in non-small cell cancer patient (NSCLC): A randomized open label, phase II clinical trial.
2022 Khurram Khan et al.	Phase 1, 2 trial of concurrent anti-PD1 and stereotactic radiosurgery for melanoma and non-small cell lung cancer brain metastases (NCT02858869).
e14006 Duan et al.	A prospective data analysis of targeted therapy combined with concurrent radiation therapy for brain metastasis from NSCLC with driver gene mutation.
e14001 Fan et al.	Consistency of O6-methylguanine-DNA methyltransferase in intracranial and extracranial lesions and the therapeutic effect of temozolomide in patients with advanced lung cancer and brain metastasis.
9068 Wade Goldman et al.	Neratinib efficacy in a subgroup of patients with EGFR exon 18-mutant non-small cell lung cancer (NSCLC) and central nervous system (CNS) involvement: Findings from the SUMMIT basket trial.

American Society of Clinical Oncology (ASCO), June 3-7, 2022 = 3 abstracts	
Abstract # First author	**Title**
9101 Chen et al.	Central nervous system efficacy of furmonertinib versus gefitinib in patients with non–small cell lung cancer with epidermal growth factor receptor mutations: Results from FURLONG study
9095 Chen et al.	Gefitinib plus chemotherapy versus gefitinib alone in untreated patients with EGFR-mutated non–small cell lung cancer and brain metastases (GAP Brain): An open-label, randomized, multicenter, phase 3 study.

American Society of Clinical Oncology (ASCO), June 3-7, 2022 = 3 abstracts	
Abstract # First author	**Title**
9096 Lu et al.	Aumolertinib activity in patients with CNS metastases and EGFR-mutated NSCLC treated in the randomized double-blind phase III trial (AENEAS).

IASLC 2021 World Conference on Lung Cancer (WCLC), September 8-14, 2021 = 7 abstracts	
Abstract # First author	**Title**
OA09.01 Carbone et al.	First-line Nivolumab + Ipilimumab + Chemo in Patients With Advanced NSCLC and Brain Metastases: Results From CheckMate 9LA
OA09.02 Nadal et al.	Atezo-Brain: Single Arm Phase II Study of Atezolizumab Plus Chemotherapy in Stage IV NSCLC With Untreated Brain Metastases
P19.02 Wang et al.	Sintilimab Plus Docetaxel in Previously Treated Advanced NSCLC, Updates on Progression-Free and Overall Survival
P40.04 Riley et al.	CNS Adverse Events and Survival in Patients with NSCLC Brain Metastases Treated With Concurrent Radiation and Immunotherapy
P40.10 Garitaonaindia et al.	Brain Metastases in Patients With Non-Small Cell Lung Cancer Treated With Immunotherapy. Real World Data From a Tertiary Hospital in Spain
P48.08 Wang et al.	The Efficacy and Clinical Survival Outcome of Different First-Line Treatments in EGFR Mutant Non-Small Cell Lung Cancer With Brain Metastases
P52.03 Ramalingam et al.	Efficacy of Sotorasib in KRAS p.G12C-Mutated NSCLC with Stable Brain Metastases: A Post-Hoc Analysis of CodeBreaK 100

IASLC 2022 World Conference on Lung Cancer (WCLC), August 6-9, 2022 = 2 abstracts	
Abstract # First author	**Title**
EP08.01-026 Swart et al.	Influence of Brain Metastases on Survival of KRASG12C Mutated Stage IV Immune Checkpoint Inhibitor Treated Non-Small Cell Lung Cancer Patients
EP08.02-142 Lee et al.	Effects of Afatinib on the Treatment and Prognosis of Brain Metastasis in Advanced EGFR Mutation (+) NSCLC

European Society of Medical Oncology (ESMO), September 1721, 2021 = 7 abstracts	
Abstract # First author	**Title**
370 Han et al.	Prospective study of apatinib combined with whole brain radiation therapy and simultaneous integrated boost for brain metastases from lung cancer
1216P Qin et al.	Effectiveness of osimertinib plus chemotherapy and avastin for EGFR-mutated advanced non-small cell lung cancer with brain metastases
1337P Zhang et al.	Clinical study of apatinib combined with radiation therapy in advanced non-small cell lung cancer patients with brain metastasis
1350P Sabouhanian et al.	Characteristics, treatment patterns and outcome of non-small cell lung cancer (NSCLC) patients presenting with brain-only metastatic disease
1221P Ma et al.	Outcomes of EGFR-mutant NSCLC patients with de novo brain metastases by upfront treatment
1201P Krebs et al.	Real-world comparative effectiveness of 1L (ALC) vs crizotinib (CRZ) in patients (pts) with ALK+ advanced NSCLC with or without baseline CNS metastases (mets)
1328P Hong et al.	Outcomes from local consolidative therapy and immune checkpoint inhibitors in metastatic non-small cell lung cancer

No relevant abstracts for brain metastases in NSCLC were identified from the following conferences:

- European Society of Medical Oncology (ESMO), September 9–13 Sep 2022
- International Conference for Pharmacoepidemiology (ICPE), August 23–25, 2021
- International Conference for Pharmacoepidemiology (ICPE), August 24–28, 2022

Clinical Trial Registers

Searching ClinicalTrials.gov and the European Union's Clinical Trials Register (EudraCT) identified 50 and 19 records of ongoing studies, respectively, as being relevant to brain metastases in the NSCLC setting.

ClinicalTrials.gov

Of the 50 records from ClinicalTrials.gov, most were phase 2 trials (32 studies). There was one phase 1/2 trial, two phase 2/3 trials, six phase 3 trials, three trials that did not specify the phase, and six observational studies. Most studies included fewer than 100 patients; nine studies included 100 to 199 patients, and 11 studies included 200 or more patients.

Of the 34 studies that included only patients with NSCLC and brain metastases, 11 included only patients with *EGFR* mutations, three included gene-negative NSCLC, and one study included patients with PD-1 antibodies; 19 studies did not specify the status of mutations or targets. An additional seven studies evaluated *EGFR*-mutated NSCLC with any CNS metastases (e.g., brain or leptomeningeal metastases), and one study was of patients with *ROS1*-mutated NSCLC with CNS metastases. The remaining eight studies comprised the following: brain metastases not specific to NSCLC (2 studies) or any NSCLC (6 studies).

Forty-eight of the 50 records from ClinicalTrials.gov evaluated treatments; two studies evaluated diagnostic tests only. Most studies evaluated at least one type of targeted therapy with or without radiotherapy or other combination treatment (29 studies). Of the studies evaluating targeted therapies, EGFR-targeting therapies under investigation included osimertinib (11 studies), almonertinib (5 studies), icotinib (2 studies),

and 1 study each of dacomitinib, lazertinib (YH25448), zorifertinib (AZD3759), and TY-9591; 2 studies used erlotinib or gefitinib as comparator treatments. Another study compared entrectinib versus crizotinib among adults with *ROS1*-positive NSCLC. *VEGF*-targeting agents included anlotinib (2 studies), apatinib (1 study), and lenvatinib (1 study). Two studies of targeted therapies did not report the specific agents under investigation.

Ten studies reported immunotherapies, most of which were PD-1/PD-L1 inhibitors, including camrelizumab (3 studies), pembrolizumab (2 studies), nivolumab (1 study), sintilimab (1 study), and tislelizumab (1 study). One study evaluated ipilimumab, a monoclonal antibody that activates the immune system by targeting CTLA-4. Two studies did not report the names of the immunotherapies under investigation.

Six studies evaluated bevacizumab in combination with a TKI or radiation therapy. One study evaluated a chemotherapy, temozolomide, with radiation therapy. Another study evaluated Endostar, an endostatin, combined with radiation therapy. Twenty studies assessed radiation therapy alone or in combination with other treatments.

European Union's Clinical Trials Register (EudraCT)

Of the 19 records from EudraCT, most were phase 3 trials (17 studies); one was a phase 3/4 trial, and one was a phase 4 trial. Nine studies included 200 or more patients, and two studies included 100 to 199 patients; eight studies did not report the sample size. Although all studies included patients with NSCLC, only two specifically mentioned including patients with brain or CNS metastases in the clinical trial record. Six studies included *ALK*-positive NSCLC, and one study each included HLA-A2–positive NSCLC, *EGFR*-positive NSCLC, and NSCLC with *ROS1* rearrangements. Two studies included patients with PD-L1 expression.

The six *ALK*-positive studies evaluated ALK-targeting agents, specifically alectinib (1 study), crizotinib (4 studies), ensartinib (1 study), and lorlatinib/PF-06463922 (2 studies); crizotinib was used as a comparator in two of the studies. The study in HLA-A2–positive NSCLC evaluated OSE-2101, a neoepitope vaccine

restricted to HLA-A2–positive patients that targets five tumor-associated antigens. The study of *EGFR*-positive NSCLC evaluated osimertinib plus chemotherapy versus chemotherapy alone. Three other studies assessed EGFR-targeting therapy alone or in combination with other treatments. The study of NSCLC with *ROS1* rearrangements compared entrectinib versus crizotinib.

Both studies that included patients with PD-L1 expression evaluated PD-1 immunotherapies, pembrolizumab or zimberelimab; a third study evaluated another PD-1 inhibitor, atezolizumab.

Four studies evaluated chemotherapy alone or in combination with radiation therapy. One study compared bevacizumab in combination with erlotinib versus erlotinib alone.