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Research article

Osimertinib is associated with improved outcomes in pre-treated non-small cell lung cancer leptomeningeal metastases: A systematic review and meta-analysiss

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ABSTRACT

Purpose: Leptomeningeal metastasis (LM) is a severe complication of non-small cell lung cancer (NSCLC). In patients with NSCLC LM harboring epidermal growth factor receptor (*EGFR*) mutations, osimertinib is favored over alternative EGFR tyrosine kinase inhibitors (TKIs). However, the efficacy of osimertinib relative to other EGFR-TKIs is not well established for patients with LM. We aimed to compare the efficacy of EGFR-TKIs in *EGFR*-mutated NSCLC LM.

Methods: This systematic review and meta-analysis performed according to PRISMA guidelines included studies of adult patients with *EGFR*-mutated NSCLC and a diagnosis of LM who received an EGFR-TKI for the treatment of LM. We searched Medline ALL, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science Core Collection. The evaluation of biases was done by using the Ottawa-Newscastle scale. The hazard ratio was used as the

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parameter of interest for overall survival (OS) and central nervous system-specific progression-free survival (PFS).
Results: 128 publications were included with 243 patients and 282 lines of EGFR-TKI for NSCLC LM that met inclusion criteria. The median PFS in patients receiving any EGFR-TKI was 9.1 months, and the median OS was 14.5 months. In univariate analyses of the entire cohort, osimertinib treatment demonstrated significantly prolonged PFS, but not OS, compared to other EGFR-TKIs. Osimertinib demonstrated significantly prolonged PFS and OS in the subset of patients who were previously treated with EGFR-TKIs, but not in EGFR-TKI naïve patients.
Conclusion: Osimertinib is associated with improved outcomes compared to other EGFR-TKIs, particularly in patients previously treated with EGFR-TKIs. An important limitation is that most patients were derived from retrospective reports. These results highlight the need for prospective studies for this difficult-to-treat patient population.

1. Introduction

Leptomeningeal metastasis (LM) is a complication in the advanced stages of cancer involving malignant cells metastasizing to the subarachnoid space surrounding the brain and spinal cord [1,2]. Alongside melanoma and breast cancer, lung cancer represents the most common solid adult cancer to metastasize to the leptomeninges [3]. The incidence of LM in non-small cell lung cancer (NSCLC) is approximately 2.8 % overall and up to 9 % in NSCLC patients whose tumor harbors epidermal growth factor receptor (*EGFR*) mutations [4]. Prior to the era of targeted therapy, patients with LM were treated with systemic chemotherapy or radiotherapy and experienced a median overall survival (mOS) of 2–5 months [5–7].

Current treatment guidelines for NSCLC LM include local and systemic approaches [8]. Whole brain radiotherapy (WBRT) is a frequently employed local therapy given that these patients are generally ineligible for surgery due to the diffuse nature of LM within the subarachnoid space. Systemic approaches for treating NSCLC LM consist of the standard therapies for NSCLC, including chemotherapy, targeted therapy, and immunotherapy [9].

When *EGFR* mutations are present, EGFR tyrosine kinase inhibitors (EGFR-TKIs) represent important components of the treatment armamentarium against NSCLC LM [10]. EGFR-TKIs approved by the United States Food and Drug Administration for *EGFR*-mutated NSCLC include the first- and second-generation EGFR-TKIs erlotinib, gefitinib afatinib, and dacomitinib, and the third-generation EGFR-TKI osimertinib [11]. First- and second-generation EGFR-TKIs have been used in various case reports and small-scale cohort studies for NSCLC LM, with prolonged therapeutic responses observed [12–16]. Third-generation EGFR-TKIs are notable for their ability to inhibit mutant EGFR proteins harboring the T790 M mutation, which constitutes the most common resistance mechanism to first- and second-generation EGFR-TKI [17–19]. Furthermore, osimertinib has demonstrated improved survival benefits compared to first-generation EGFR-TKIs for primary *EGFR*-mutated NSCLC in phase III clinical trials [20,21]. Osimertinib has also shown the ability to reach therapeutic concentrations in the central nervous system (CNS) with improved progression-free survival (PFS) in *EGFR*--mutated NSCLC patients with CNS parenchymal metastases versus first-generation EGFR-TKIs [9,18,20,22,23].

Given that LM is a relatively uncommon presentation of NSCLC, most studies on EGFR-TKIs for NSCLC have focused on advanced primary disease and CNS parenchymal metastases [20–22,24]. There are limited studies specifically evaluating the efficacy of osimertinib for NSCLC LM, predominantly consisting of smaller-scale cohort studies [25–31]. Consequently, the efficacy of osimertinib for NSCLC LM compared to previous-generation EGFR-TKIs remains unclear, with no studies, to our knowledge, directly comparing first-, second-, and third-generation EGFR-TKIs. To address this gap, we conducted a systematic review and meta-analysis of individualized patient data to provide insights into the activity of different generations of EGFR-TKIs in the context of EGFR-mutated NSCLC LM.

2. Methods

2.1. Inclusion and exclusion criteria

Inclusion criteria consisted of the following: published reports of adult *EGFR*-mutated NSCLC, defined by next generation sequencing, with LM diagnosed by magnetic resonance imaging (MRI) or by cerebrospinal fluid (CSF) cytology, receiving an EGFR-TKI specifically for the treatment of LM. Therapies evaluated included the first-generation EGFR-TKIs erlotinib, gefitinib, and icotinib; the second-generation EGFR-TKIs afatinib and dacomitinib; and the third-generation EGFR-TKIs osimertinib, zorifertinib and furmonertinib (Supplemental Table S1).

2.2. Search strategy

We searched the literature across all databases of Medline (Medline, Medline Epub Ahead of Print, and In-Process & Other Non-Indexed Citations), Embase, Cochrane Central Register of Controlled Trials, Scopus, and the Web of Science Core Collection from January 1964 to December 2021. The complete search strategy is available in Appendix A. Data from published conference abstracts were also included in this meta-analysis. Any additional publications or data sourced by the authors beyond the initial search were integrated into the systematic review where relevant. The study protocol was performed according to the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) guidelines and prospectively registered on PROSPERO (ID: CRD42021292539) [32–34].

2.3. Data extraction and management

The Rayyan software was employed for abstract screening. Each abstract was screened by two independent reviewers (www.rayyan.ai). Three reviewers (AML, SMM, MD) resolved conflicts through internal discussions. Patient demographics and outcomes were extracted by the lead author; due to the added complexity of data in some publications screened, a subset (25 %) of abstracts was extracted by a second author (AML) to confirm accuracy. Additionally, Chinese, and Japanese reports with English titles that were included in the original search were translated and extracted by the lead author. Following extraction of all available data from the publications included in the meta-analysis, requests for missing data were sent to the original authors of each publication through two separate email prompts spaced seven days apart.

We categorized the patients included in published reports based on generations of EGFR-TKI into first-, second-, and third-generation EGFR-TKIs, as previously described [11]. Additionally, when patients received multiple EGFR-TKIs simultaneously ($N = 4$), the patient-line of therapy was assigned to the most recent-generation EGFR-TKI given.

EGFR mutations were classified in the following ways: by mutation location (i.e. exon 18, exon 19, exon 20, and exon 21), by presence or absence of previously described EGFR-TKI on-target resistance mutations (i.e. T790 M, C797X, L718Q, E884K, L747X, G724S, and K754E), and by type of mutation (i.e. insertion, deletion, and point mutation) [35]. We also compared *EGFR* classical driver mutations (i.e. exon 19 deletion and L858R), and atypical *EGFR* driver mutations (i.e. G719X, exon 19 insertion, exon 20 insertion, S768I, L861Q, SEPT14-EGFR fusion, and intron 17–28 duplication), which have been previously classified by Robichaux et al. [36].

2.4. Primary outcomes

The co-primary outcomes of interest were CNS-specific PFS, and OS. Both endpoints were calculated from the start of EGFR-TKI therapy for LM. Endpoints were defined as the following: CNS-specific PFS was determined based on CNS-specific disease progression (i.e., MRI or CSF analysis-proven progression), or death of the patient per the authors of the primary paper. Causes of progression were further classified as death of the patient from any cause while on treatment, progression of LM confirmed by MRI or CSF, progression of intraparenchymal brain metastases, and CNS progression of either LM or brain metastases that was not specified by the authors of the primary paper (Supplemental Table S2).

2.5. Quality (risk of bias) assessment

In order to evaluate the methodological quality of the studies in the meta-analysis, we employed a tool previously described adapted from the Newcastle-Ottawa scale, tailored for assessing case reports and case series, allowing to assess the selection and representativeness of cases, as well as the ascertainment of outcomes and exposure [37]. Each parameter evaluated earns one point if the study explicitly reports the relevant information. A study is considered to be of good quality (i.e., low risk of bias) if it meets all five criteria, of moderate quality if it meets four criteria, and of poor quality (high risk of bias) if it meets three or fewer criteria (Supplemental Fig. S1) [38,39].

2.6. Statistical analyses

We conducted one-stage meta-analyses, pooling individual patient data from all studies included. Patient characteristics were then compared between those who received third-generation EGFR-TKI and those who received first- and second-generation EGFR-TKIs with Fisher's Exact test and Pearson's X^2. The hazard ratio (HR) served as the primary parameter of interest for OS and CNS-specific PFS. Univariate logistic regression models were utilized to ascertain the HR between the groups of interest along with its corresponding 95 % confidence interval (CI). Multi-level mixed-effects Cox proportional hazards regression models, integrating individual studies as a random effect, were applied.

Multivariate Cox proportional hazards regression models were employed to estimate adjusted CNS-specific PFS and OS (aPFS and aOS), incorporating a multi-level mixed-effects Cox proportional hazards regression model that accounted for individual studies as a random effect. All variables with $P < 0.05$ in univariate analysis were incorporated into the initial multivariate model. Backward stepwise selection was employed to eliminate variables deemed insignificant. The final model included all variables with $P < 0.05$. For aPFS, the initial model included sex, prospective versus retrospective studies, previous lines of therapy (0–2 versus 3 or more), previous EGFR-TKI use, concurrent extracranial metastasis, concurrent intracranial metastasis, ECOG status (0–2 versus 3–4), treatment with osimertinib, and treatment with afatinib. In the multivariate model for aPFS, sex and prior EGFR-TKI use were identified as the statistically significant variables. For aOS, the initial multivariate model included year of study (2018 or after versus before 2018), previous lines of therapy (0–2 versus 3 or more), previous EGFR-TKI use, concurrent extracranial metastasis, concurrent intracranial metastasis, ECOG status (0–2 versus 3–4), MRI-only diagnosis, CSF-only diagnosis, and treatment with afatinib. In the multivariate model, following the analysis, ECOG status and prior lines of therapy emerged as the statistically significant variables influencing adjusted aOS.

Correlation analyses between PFS and OS were conducted utilizing linear regression and Pearson's X^2. In cases where performance

status was indicated by the Karnofsky Performance Status score, it was converted to Eastern Cooperative Oncology Group (ECOG) status employing a conversion scale previously outlined in the literature [40].

Survival curves were depicted and assessed using the Kaplan-Meier method and the log-rank test, which were performed to compare the CNS-specific PFS and OS of osimertinib versus other EGFR-TKIs; afatinib versus other EGFR-TKIs; and presence versus absence of concurrent chemotherapy. Additionally, Kaplan-Meier survival curves and the log-rank test were conducted for subgroup analyses. These survival curves included analysis of CNS-specific PFS and OS on osimertinib compared to other EGFR-TKIs in patients having been treated with prior EGFR-TKIs and those without prior EGFR-TKI treatment; afatinib compared to other EGFR-TKIs in patients having been treated with prior EGFR-TKIs and those without prior EGFR-TKI treatment; and route of administration (intravenous versus intrathecal) of concurrent chemotherapy.

STATA v17 was employed for statistical analyses (StataCorp LLC, College Station, Texas, USA).

3. Results

3.1. Characteristics of included studies and patients

We initially identified 7780 articles potentially eligible for inclusion in the search. Following the initial screening process, which involved removing ineligible articles and supplementing with studies from authors' files, a total of 128 publications were ultimately included in the meta-analysis (Appendix B and Appendix C). 106 of the publications were case reports [14–16,41–142]. 13 of the publications were case series [143–155]. 7 of the publications were retrospective studies [13,25–28,156,157]. Finally, 2 of the publications were prospective studies [12,29]. This consisted of a total of 243 patients with *EGFR*-mutated lung cancer LM who received a total of 282 patient-lines of EGFR-TKI therapy for the treatment of LM (Fig. 1). Additionally, following preliminary

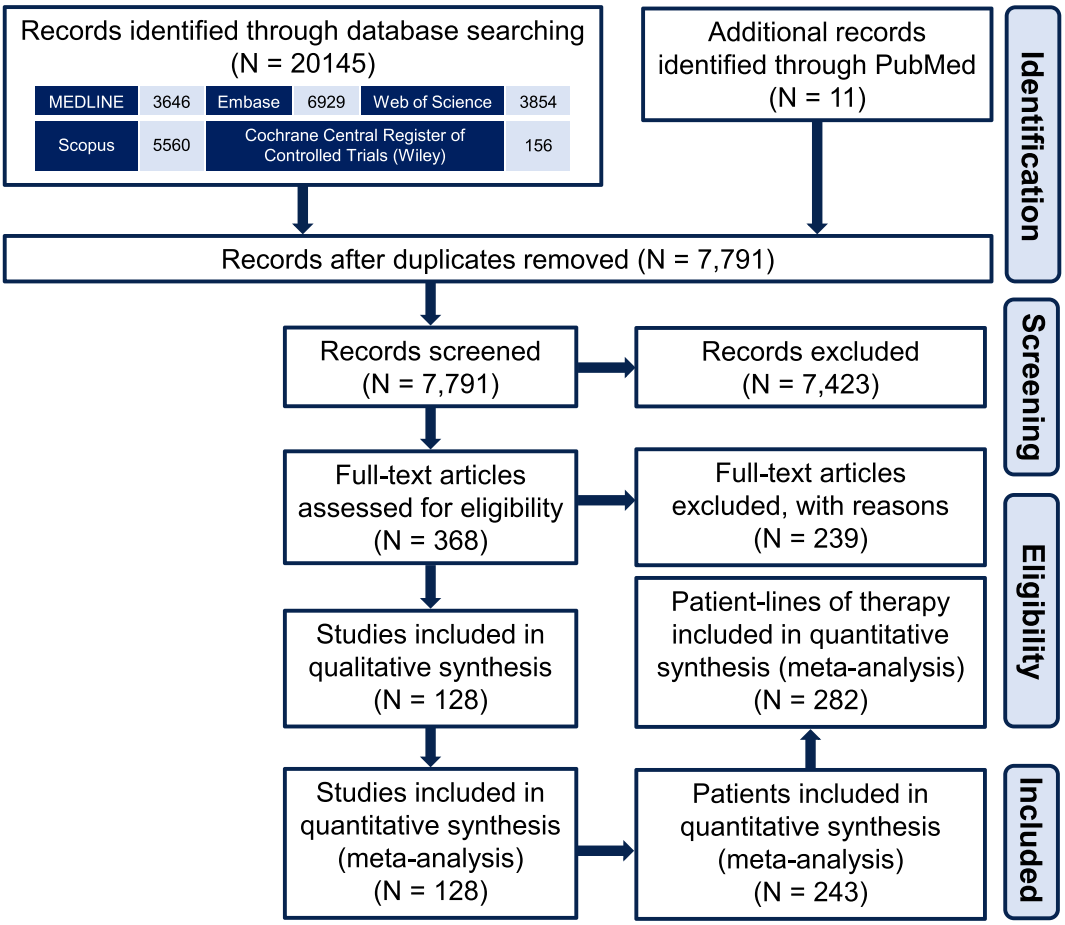

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram demonstrating search and inclusion of studies for meta-analysis. The flow diagram demonstrates the 20 145 records identified through the initial search of different databases. Repeated searches using the search strategy outlined in Appendix A were performed on Pubmed during the subsequent data extraction phase, identifying an additional 11 records that respected our inclusion criteria. Duplicate removal and further screening had identified 368 eligible articles. 128 articles comprising of 282 patient-lines of therapy were included for the final analysis.

Table 1
Individual patient characteristics.

Variable	Entire Cohort No. (%)	Third Generation EGFR TKI cohort (%)	First and Second Generation EGFR TKI cohort (%)	P (Fisher's exact)	Pearson's $\chi 2$
Patient-lines of therapy	**282 (100)**	**125 (44.3)**	**157 (55.7)**		
		Study characteristics			
Geographic location					
North America	40 (14.2)	15 (12.0)	25 (15.9)	0.394	8.045, P =
Europe	10 (3.5)	4 (3.2)	6 (3.8)	1	0.154
Asia	222 (78.7)	100 (80.0)	122 (77.7)	0.77	
Australia	10 (3.5)	6 (4.8)	4 (2.5)	0.345	
Year of study					
<2018	125 (44.3)	10 (8.0)	115 (73.2)	**<0.0001**	
≥2018	157 (55.7)	115 (92.0)	42 (26.8)		
Sample size					
<5	188 (66.7)	63 (50.4)	125 (79.6)	**<0.0001**	
≥5	94 (33.3)	62 (49.6)	32 (20.4)		
Risk of bias					
≤3	113 (40.1)	50 (40.0)	63 (40.1)	1	
4, 5	169 (59.9)	75 (60.0)	94 (59.9)		
Study type					
Retrospective	258 (91.5)	112 (89.6)	146 (93.0)	0.512	
Prospective	24 (8.5)	13 (10.4)	11 (7.0)		
		Patient characteristics			
Sex					
Male	112 (39.7)	58 (46.4)	54 (34.4)	**0.006**	
Female	157 (55.7)	54 (43.2)	103 (65.6)		
Unknown	13 (4.6)	13 (10.4)	0 (0)		
Age, years					
<60	135 (47.9)	61 (48.8)	74 (47.1)	0.266	
≥60	134 (47.5)	51 (40.8)	83 (52.9)		
Unknown	13 (4.6)	13 (10.4)	0 (0)		
Lines of therapy					
0–2	124 (44.0)	51 (40.8)	73 (46.5)	0.902	
≥3	145 (51.4)	61 (48.8)	84 (53.5)		
Unknown	13 (4.6)	13 (10.4)	0 (0)		
Prior EGFR TKI					
No	73 (25.9)	23 (18.4)	50 (31.8)	**0.014**	
Yes	209 (74.1)	102 (81.6)	107 (68.2)		
Concurrent extracranial metastases					
No	58 (20.6)	52 (41.6)	33 (21.0)	0.455	
Yes	190 (67.4)	94 (75.2)	96 (61.1)		
Unknown	34 (12.1)	6 (4.8)	28 (17.8)		
Concurrent intracranial metastases					
No	91 (32.3)	46 (36.8)	45 (28.7)	0.152	
Yes	171 (60.6)	70 (56.0)	101 (64.3)		
Unknown	20 (7.1)	9 (7.2)	11 (7.0)		
Location of LM					
Brain	213 (75.5)	89 (71.2)	124 (79.0)	0.345	0.908, P =
Spinal cord	6 (2.1)	3 (2.4)	3 (1.9)	0.7	0.635
Both	13 (4.6)	7 (5.6)	6 (3.8)	0.403	
Unknown	51 (18.1)	27 (21.6)	24 (15.3)		
ECOG status					
0–2	78 (27.7)	43 (34.4)	35 (22.3)	**0.012**	
3 and 4	70 (24.8)	24 (19.2)	46 (29.3)		
Unknown	134 (47.5)	58 (46.4)	76 (48.4)		
Smoking status					
Never	101 (35.8)	30 (24.0)	71 (45.2)	0.05	
Current/Former	30 (10.6)	15 (12.0)	15 (9.6)		
Unknown	151 (53.5)	80 (64.0)	71 (45.2)		
Cancer type					
EGFR-mutant lung adenocarcinoma	278 (98.6)	121 (96.8)	157 (100.0)	**0.037**	
EGFR-mutant lung squamous cell carcinoma	4 (1.4)	4 (3.2)	0 (0)		
		Mutational status			
Specific mutations of interest					
Exon 19 deletion	133 (47.2)	55 (44.0)	78 (49.7)	0.197	
L858R point mutation	109 (38.7)	52 (41.6)	57 (36.3)	0.211	
T790 M point mutation	50 (17.7)	39 (31.2)	11 (8.7)	**<0.0001**	
Mutational status by exon location					
Exon 18 mutation	9 (3.2)	3 (2.4)	6 (3.8)	1	

(*continued on next page*)

Table 1 (*continued*)

Variable	Entire Cohort No. (%)	Third Generation EGFR TKI cohort (%)	First and Second Generation EGFR TKI cohort (%)	P (Fisher's exact)	Pearson's χ2
Exon 19 mutation	133 (47.2)	54 (43.2)	79 (50.3)	0.377	
Exon 20 mutation	2 (0.7)	2 (1.6)	0 (0)	0.083	
Exon 21 mutation	109 (38.7)	51 (40.8)	58 (36.9)	0.31	
Resistance mutations	61 (21.6)	40 (32.0)	21 (13.4)	**<0.0001**	
Mutational status by classical versus atypical					
Classical mutations	237 (84.0)	103 (82.4)	134 (85.4)	0.642	
Atypical mutations	28 (9.9)	10 (8.0)	18 (11.5)		
Mutational status by classical versus atypical					
Deletion mutations	133 (47.2)	55 (44.0)	78 (49.7)	0.449	1.484, P =
Insertion mutations	3 (1.1)	2 (1.6)	1 (0.6)	0.584	0.476
Point mutations	121 (42.9)	57 (45.6)	64 (40.8)	0.377	
		Diagnostic characteristics			
Method of LM diagnosis					
Magnetic resonance imaging only	78 (27.7)	37 (29.6)	41 (26.1)	1	3.859, P =
Cerebrospinal fluid only	73 (25.9)	41 (32.8)	32 (20.4)	0.098	0.145
Both magnetic resonance imaging and cerebrospinal fluid	105 (37.2)	43 (34.4)	62 (39.5)	0.098	
Unknown	27 (9.6)	4 (3.2)	23 (14.6)		
Time from primary cancer diagnosis to LM diagnosis, months					
<12	81 (28.7)	25 (20.0)	56 (35.7)	0.136	
≥12	117 (41.5)	49 (39.2)	68 (43.3)		
Unknown	84 (29.8)	51 (40.8)	33 (21.0)		
Chemotherapy simultaneously with EGFR TKI					
No	210 (74.5)	95 (76.0)	115 (732)	0.259	
Yes	48 (17.0)	17 (13.6)	31 (19.7)		
Unknown	24 (8.5)	13 (10.4)	11 (7.0)		
Route of administration for chemotherapy concurrently to EGFR TKI					
Intravenous or oral only	17 (6.0)	7 (5.6)	10 (6.4)	0.547	4.693, P =
Intrathecal only	23 (8.2)	5 (4.0)	18 (11.5)	0.227	0.096
Intrathecal and intravenous or oral	8 (2.8)	5 (4.0)	3 (1.9)	0.112	
Radiotherapy for LM					
Yes	154 (19.1)	20 (16.0)	34 (21.7)	0.355	
No	201 (71.3)	89 (71.2)	112 (71.3)		
Unknown	24 (2.8)	13 (10.4)	11(7.0)		
Radiotherapy for LM					
Stereotactic radiosurgery	5 (1.8)	3 (2.4)	2 (1.3)	0.369	1.581, P =
Whole-brain radiotherapy	45 (16.0)	16 (12.8)	29 (18.5)	0.195	0.209
Whole-brain radiotherapy and stereotactic	1 (0.4)	1 (0.8)	0 (0)	0.392	
Received brain radiotherapy, but unknown type	3 (1.1)	0 (0)	3 (1.9)		

NOTE. Bold values indicate P < 0.05. **Abbreviations:** LM, leptomeningeal metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group.

screening of eligible articles and after contacting authors of all studies with potentially includible data, we were not able to extract data from 55 potentially eligible publications, including 15 prospective studies, 35 retrospective studies, and 5 case series or case reports (Appendix D and Appendix E).

Detailed characteristics of patients receiving third-generation EGFR-TKIs versus those receiving first- or second-generation EGFR-TKIs can be found in Table 1. A risk of bias assessment was conducted for all studies included in the meta-analysis, utilizing a 5-point scale (Supplemental Figure S1).

Patients receiving any EGFR-TKI for the treatment of NSCLC LM experienced a CNS-specific median PFS (mPFS) of 9.1 months (Table 2) and a mOS of 14.5 months (Table 3). Among the 243 individual patients, accounting for 282 patient-lines of therapy, 120 lines of therapy consisted of first-generation EGFR-TKI, 37 consisted of second-generation EGFR-TKI, and 125 consisted of third-generation EGFR-TKI (Table 1). In the patient-lines of therapy where CNS-specific PFS was available (N = 272), we observed a significant correlation between CNS-specific PFS and OS (Pearson's $R^2 = 0.37$, $P < 0.0001$) (Supplemental Fig. S2 A). This significant correlation was maintained when analyses were restricted to patients with documented death, or whose progression cases were not restricted to death (Supplemental Fig. S2 B-D and Supplemental Table S2).

3.2. Variables associated with PFS and OS in EGFR-mutated lung cancer LM patients

In univariate analyses, the following variables were associated with shortened CNS-specific PFS and OS: patients who received 3 or more total lines of therapy since initial diagnosis of NSCLC (PFS: HR = 1.72, 95 % CI: 1.21–2.46, $P = 0.003$; OS: HR = 2.37, 95 % CI: 1.60–3.52, $P < 0.001$); prior treatment with EGFR-TKIs (PFS: HR = 2.23, 95 % CI: 1.49–3.33, $P < 0.001$; OS: HR = 2.41, 95 % CI: 1.53–3.79, $P < 0.001$); presence of concurrent extracranial metastases (PFS: HR = 1.58, 95 % CI: 1.05–2.39, $P = 0.028$; OS: HR = 1.96,

Table 2
CNS-specific progression-free survival rates associated with clinical variables.

CNS-SPECIFIC PROGRESSION-FREE SURVIVAL	Patient lines of therapy	Median OS (months)	Univariable Hazard Ratio	Univariable 95 % CI	Univariable P value	Adjusted Hazard Ratio	Multivariable 95 % CI	Adjusted P Value
Entire Cohort	272	9.1						
			Study characteristics					
Geographic location								
America	40	7.6	1.361	0.832–2.225	0.219			
Europe	10	6	1.293	0.465–3.303	0.669			
Asia	212	9.4	0.788	0.507–1.224	0.288			
Australia	10	12	0.75	0.242–2.335	0.621			
Year of study								
<2018	125	8	0.691	0.473–1.008	0.055			
≥2018	147	10						
Sample size								
<5	187	9.3	1.282	0.796–2.067	0.307			
≥5	85	9.1						
Risk of bias								
≤3	113	9.1	0.773	0.510–1.172	0.226			
4, 5	159	9.2						
Study type								
Retrospective	248	9.5	2.215	1.042–4.709	**0.039**			
Prospective	24	6.5						
			Patient characteristics					
Sex								
Female	153	8	0.690	0.487–0.977	**0.037**	0.687	0.488–0.968	**0.032**
Male	106	10						
Age, years								
<60	131	9	0.781	0.549–1.109	0.167			
≥60	128	9.3						
Lines of therapy								
0–2	120	12	1.723	1.209–2.456	**0.003**			
≥3	139	7.5						
Previous EGFR TKI								
No	71	13	2.231	1.494–3.334	**<0.001**	2.152	1.577–3.134	**<0.001**
Yes	201	7.6						
Concurrent extracranial metastasis								
No	56	12	1.583	1.050–2.386	**0.028**			
Yes	182	8						
Concurrent intracranial metastasis								
No	84	12	1.451	1.005–2.094	**0.047**			
Yes	168	8						
Location of LM								
Brain	206	9	1.162	0.591–2.284	0.663			
Spinal cord	6	9	1.085	0.415–2.836	0.868			
Both	10	11	0.717	0.292–1.763	0.496			
ECOG status								
0–2	74	9.5	1.817	1.110–2.976	**0.018**			
3,4	65	7						
Smoking status								
Never	100	9.6	0.822	0.453–1.488	0.517			
Current/Former	30	9.4						
Cancer type								
EGFR-mutant lung adenocarcinoma	268	9.1	0.663	0.147–2.988	0.592			
EGFR-mutant lung squamous cell carcinoma	4	12						
			Mutational status					
Specific mutations of interest								
Exon 19 deletion	128	8	1.085	0.772–1.525	0.638			
L858R point mutation	103	8	1.216	0.862–1.715	0.265			
T790 M point mutation	50	8	1.252	0.786–1.995	0.344			
Mutational status by exons								
Exon 18 mutation	10	N/A	0.368	0.125–1.082	0.069			
Exon 19 mutation	129	9	1.01	0.712–1.432	0.995			
Exon 20 mutation	3	8	0.95	0.205–4.408	0.948			
Exon 21 mutation	106	8	1.153	0.811–1.639	0.428			
Resistance mutations	61	8	1.113	0.721–1.717	0.63			

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Table 2 (*continued*)

CNS-SPECIFIC PROGRESSION-FREE SURVIVAL	Patient lines of therapy	Median OS (months)	Univariable Hazard Ratio	Univariable 95 % CI	Univariable P value	Adjusted Hazard Ratio	Multivariable 95 % CI	Adjusted P Value
Mutational status by classical versus atypical								
Classical mutations	228	9	0.668	0.338–1.318	0.244			
Atypical mutations	19	10.3						
Mutational status by mechanism of mutation								
Deletion mutations	128	9	0.987	0.696–1.400	0.942			
Insertion mutations	3	6	2.144	0.583–7.889	0.251			
Point mutations	115	9	0.982	0.693–1.393	0.920			
Diagnostic characteristics								
Method of LM diagnosis								
Magnetic resonance imaging only	82	11	0.82	0.5786–1.163	0.266			
Cerebrospinal fluid only	68	9.9	1.115	0.7800–1.594	0.55			
Both magnetic resonance imaging and cerebrospinal fluid	107	9	1.039	0.750–1.440	0.818			
Time from primary diagnosis to LM diagnosis, months								
<12 months	81	10	1.108	0.764–1.606	0.589			
≥12 months	116	9.6						
Treatments								
Type of therapy								
1st generation EGFR TKI	119	9	1.141	0.795–1.638	0.474			
2nd generation EGFR TKI	37	5.6	1.922	1.160–3.186	**0.01**			
3rd generation EGFR TKI	115	11	0.63	0.432–0.919	**0.016**			
Regimens including each of the following therapies								
1st generation EGFR TKI								
Erlotinib	86	9	1.179	0.804–1.729	0.399			
Gefitinib	32	10	1.058	0.649–1.726	0.821			
Icotinib	4	12	0.383	0.0799–1.832	0.229			
2nd generation EGFR TKI								
Afatinib	33	5.6	2.000	1.176–3.401	**0.01**			
Dacomitinib	4	12	1.257	0.283–5.583	0.764			
3rd generation EGFR TKI								
Osimertinib	112	11	0.620	0.424–0.908	**0.014**			
Zorifertinib	2	3	3.800	0.488–29.584	0.202			
Furmonertinib	1	N/A	N/A	N/A	N/A			
EGFR TKI dosing regimens								
Osimertinib 80 mg daily	84	12	1.430	0.666–3.068	0.359			
Osimertinib 160 mg daily	14	9						
Chemotherapy for LM simultaneously to EGFR TKI								
No	201	9.1	0.699	0.451–1.085	0.111			
Yes	47	10						
Route of administration for chemotherapy concurrently to EGFR TKI								
Intravenous or oral only	17	9.6	1.35	0.624–2.921	0.446			
Intrathecal only	24	12	0.614	0.272–1.382	0.239			
Intrathecal and intravenous or oral	7	9.7	1.287	0.441–3.751	0.644			
Concurrent bevacizumab for LM								
No	248	9	0.706	0.379–1.317	0.274			
Yes	24	11.9						
Radiotherapy for LM								
No	195	9.3	0.878	0.578–1.334	0.543			
Yes	53	10						
Type of radiotherapy for LM								
Stereotactic radiosurgery	4	6	1.442	0.337–6.169	0.622			
Whole-brain radiotherapy	45	10	0.543	0.16–1.840	0.327			

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Table 2 (*continued*)

CNS-SPECIFIC PROGRESSION-FREE SURVIVAL	Patient lines of therapy	Median OS (months)	Univariable Hazard Ratio	Univariable 95 % CI	Univariable P value	Adjusted Hazard Ratio	Multivariable 95 % CI	Adjusted P Value
Both stereotactic and whole-brain radiotherapies	1	N/A	N/A	N/A	N/A			

NOTE. Univariate and multivariate hazard ratios, 95 % CIs, and P-values calculated with a multilevel mixed-effects logistic regression model with article as the random-effects variable. Bold values indicate P < 0.05. **Abbreviations:** CI, confidence interval; CNS, central nervous system; mPFS, **median** progression-free survival; LM, leptomeningeal metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group.

95 % CI: 1.20–3.43, $P = 0.018$), presence of concurrent intracranial metastases (PFS: HR = 1.45, 95 % CI: 1.01–2.09, $P = 0.047$; OS: HR = 1.97, 95 % CI: 1.25–3.08, $P = 0.003$), and ECOG status of 3–4 (PFS: HR = 1.82, 95 % CI: 1.11–2.99, $P = 0.018$; OS: HR = 2.49, 95 % CI: 1.51–4.10, $P < 0.001$) (Tables 2 and 3).

Male sex was associated with prolonged CNS-specific PFS (HR = 0.69, 95%CI: 0.49–0.98, $P = 0.037$). Patients derived from reports published after 2018 (HR = 0.53, 95%CI: 0.33–0.85, $P = 0.009$) and having received a diagnosis of LM by MRI-only (HR = 0.63, 95% CI: 0.39–0.997, $P = 0.049$) experienced prolonged OS. Diagnosis of LM by CSF-only analysis was associated with shortened OS (HR = 1.72, 95%CI: 1.01–2.94, $P = 0.046$) (Tables 2 and 3).

In multivariate analysis, male sex (HR = 0.69, 95 % CI: 0.49–0.97, $P = 0.032$) was independently associated with significantly prolonged CNS-specific PFS (Table 2). Total lines of therapy received (3 or more) (HR = 2.41, 95 % CI: 1.55–3.76, $P < 0.001$) and ECOG status of 3–4 (HR = 2.00, 95 % CI: 1.29–3.11, $P = 0.002$) remained significantly associated with shortened OS (Table 3). Multivariate analyses also demonstrated that prior EGFR-TKI use (HR = 2.15, 95 % CI: 1.58–3.13, $P < 0.001$) was associated with significantly shortened OS.

3.3. Osimertinib is associated with improved outcomes compared to alternative EGFR-TKIs, particularly in EGFR-TKI pre-treated patients

Osimertinib treatment was associated with significantly prolonged CNS-specific PFS compared to all previous-generation EGFR-TKIs and showed a non-significant trend towards prolonged OS (PFS: HR = 0.62, 95 % CI: 0.42–0.91, $P = 0.014$; OS: HR = 0.72, 95 % CI: 0.46–1.14, $P = 0.16$) (Log rank: $P = 0.014$ and $P = 0.185$, respectively) (Tables 2 and 3) (Fig. 2 A-B). CNS-specific PFS and OS were both significantly prolonged when separately comparing all three generations of EGFR-TKIs (Log rank: $P = 0.004$ and $P = 0.043$, respectively) (Fig. 2 C-D). Osimertinib was not associated with CNS-specific PFS, or prolonged OS when compared to other EGFR-TKI in LM patients who did not receive prior EGFR-TKIs (Log rank: $P = 0.304$ and $P = 0.744$, respectively) (Supplemental Fig. S3 A-B). These findings were similarly observed when comparing all three generations of EGFR-TKIs for CNS-specific PFS and OS (Log rank: $P = 0.540$ and $P = 0.872$, respectively) (Supplemental Fig. S3 C-D). However**,** osimertinib was associated with significantly prolonged CNS-specific PFS (Log rank $P = 0.003$) and OS (Log rank $P = 0.008$) in LM patients who were previously treated with EGFR-TKI therapy (Fig. 3 A-B). Significantly different CNS-specific PFS and OS were also observed when comparing all three generations of EGFR-TKIs (Log rank $P = 0.0001$ and $P = 0.0009$, respectively) (Fig. 3 C-D).

In contrast to osimertinib, patients treated with afatinib experienced shortened CNS-specific PFS and OS compared to all other EGFR-TKIs (PFS: HR = 2.00, 95 % CI: 1.18–3.40, $P = 0.01$; OS: HR = 2.22, 95 % CI: 1.11–4.46, $P = 0.024$) (Log rank $P = 0.003$ and $P = 0.045$, respectively) (Tables 2 and 3) (Supplemental Fig. S4 A-B). Afatinib treatment demonstrated similar CNS-specific PFS and OS versus other EGFR-TKIs when patients had no prior EGFR-TKI treatment (Log rank $P = 0.898$ and $P = 0.631$, respectively), but was associated with shortened CNS-specific PFS and OS in NSCLC LM patients having received prior EGFR-TKI therapy (Log rank $P < 0.0001$ and $P = 0.0001$, respectively) (Supplemental Fig. S4 C–F).

3.4. Osimertinib is associated with improved outcomes compared to alternative EGFR-TKIs in patients with EGFR exon 19 deletion mutations, but not EGFR L858R point mutations

Osimertinib was associated with significantly prolonged CNS-specific PFS and OS compared to other EGFR-TKIs in LM patients with *EGFR* exon 19 deletion mutation (Log rank $P = 0.002$ and $P = 0.0252$, respectively) (Supplemental Fig. S5 A-B). In contrast, osimertinib demonstrated no significant difference in CNS-specific PFS and OS compared to other EGFR-TKIs in LM patients with *EGFR* L858R point mutation (Log rank $P = 0.387$ and $P = 0.609$, respectively) (Supplemental Fig. S5 C-D). Moreover, osimertinib demonstrated prolonged CNS-specific PFS, but not OS, in LM patients with the acquired *EGFR* T790 M point mutation (Log rank $P = 0.003$ and $P = 0.380$, respectively) (Supplemental Fig. S5 E-F).

3.5. Concurrent non-EGFR-TKI treatments are not associated with improved outcomes in EGFR-mutated NSCLC LM patients

Concurrent administration of chemotherapy, administered either intrathecally, intravenously, or orally, alongside EGFR-TKI therapy was not associated with differential CNS-specific PFS or OS (PFS: HR = 0.70, 95 % CI: 0.45–1.09, $P = 0.11$; OS: HR = 0.73, 95 % CI: 0.41–1.31, $P = 0.29$) (Log rank $P = 0.091$ and $P = 0.404$, respectively) (Tables 2 and 3) (Supplemental Fig. S6 A-D).

Table 3
Overall survival rates associated with clinical variables.

OVERALL SURVIVAL	Patient lines of therapy	Median OS (months)	Univariable Hazard Ratio	Univariable 95 % CI	Univariable P value	Adjusted Hazard Ratio	Multivariable 95 % CI	Adjusted P Value
Entire Cohort	280	14.5						
				Study characteristics				
Geographic location								
America	40	15.3	1.024	0.528–2.112	0.946			
Europe	10	11.5	2.033	0.622–6.642	0.24			
Asia	220	14.5	0.898	0.492–1.642	0.727			
Australia	10	21	0.62	0.130–2.959	0.548			
Year of study								
<2018	125	11.5	0.527	0.325–0.854	**0.009**			
≥2018	155	18						
Sample size								
<5	186	15	1.134	0.588–2.109	0.74			
≥5	94	14.5						
Risk of bias								
≤3	111	14	0.677	0.400–1.148	0.148			
4, 5	169	15						
Study type								
Retrospective	256	15.3	2.556	0.866–7.544	0.089			
Prospective	24	7.5						
				Patient characteristics				
Sex								
Female	157	13.67	0.709	0.478–1.053	0.088			
Male	110	19						
Age, years								
<60	134	14.5	0.817	0.549–1.216	0.320			
≥60	133	15.8						
Lines of therapy								
0–2	122	20	2.371	1.598–3.519	**<0.001**	2.413	1.551–3.755	**<0.001**
≥3	145	11						
Previous EGFR TKI								
No	73	21	2.412	1.533–3.794	**<0.001**			
Yes	207	13.67						
Concurrent extracranial metastasis								
No	57	34	1.958	1.120–3.425	**0.018**			
Yes	189	14.5						
Concurrent intracranial metastasis								
No	90	21.5	1.965	1.254–3.077	**0.003**			
Yes	170	13.7						
Location of LM								
Brain	212	14.5	0.671	0.329–1.369	0.273			
Spinal cord	6	14.5	1.123	0.421–2.999	0.817			
Both	13	11	2.229	0.788–6.304	0.131			
ECOG status								
0–2	78	16.5	2.486	1.507–4.100	**<0.001**	2.000	1.288–3.105	**0.002**
3,4	69	10						
Smoking status								
Never	101	15	0.582	0.225–1.506	0.264			
Current/Former	29	N/A						
Cancer type								
EGFR-mutant lung adenocarcinoma	276	14.5	0.494	0.0574–4.244	0.520			
EGFR-mutant lung squamous cell carcinoma	4	N/A						
				Mutational status				
Specific mutations of interest								
Exon 19 deletion	131	15.1	0.937	0.639–1.373	0.737			
L858R point mutation	109	14	1.310	0.890–1.928	0.172			
T790 M point mutation	50	13.7	0.522	0.696–2.042	0.522			
Mutational status by exons								
Exon 18 mutation	10	N/A	0.474	0.130–1.725	0.257			
Exon 19 mutation	132	16.25	0.906	0.610–1.345	0.624			
Exon 20 mutation	3	13.5	0.518	0.0566–4.735	0.560			
Exon 21 mutation	111	14	1.179	0.790–1.758	0.420			
Acquired mutation	61	12	1.22	0.740–2.012	0.436			

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Table 3 (*continued*)

OVERALL SURVIVAL	Patient lines of therapy	Median OS (months)	Univariable Hazard Ratio	Univariable 95 % CI	Univariable P value	Adjusted Hazard Ratio	Multivariable 95 % CI	Adjusted P Value
Mutational status by classical versus atypical								
Classical mutations	235	14	0.872	0.393–1.936	0.736			
Atypical mutations	20	16.5						
Mutational status by mechanism of mutation								
Deletion mutations	131	15.1	0.872	0.587–1.295	0.497			
Insertion mutations	3	13.5	2.006	0.291–13.878	0.480			
Point mutations	121	14	1.132	0.762–1.681	0.540			
				Diagnostic characteristics				
Method of LM diagnosis								
Magnetic resonance imaging only	78	17.3	0.626	0.3935–0.9973	**0.049**			
Cerebrospinal fluid only	73	13.6	1.724	1.010–2.942	**0.046**			
Both magnetic resonance imaging and cerebrospinal fluid	107	17	1.058	0.657–1.703	0.817			
Time from primary diagnosis to LM diagnosis, months								
<12 months	80	15.1	0.974	0.566–1.679	0.925			
≥12 months	116	16.25						
				Treatments				
Type of therapy								
1st generation EGFR TKI	118	14	1.017	0.657–1.574	0.94			
2nd generation EGFR TKI	37	9.2	2.154	1.105–4.199	**0.024**			
3rd generation EGFR TKI	124	17	0.699	0.443–1.103	0.124			
Regimens including each of the following therapies								
1st generation EGFR TKI								
Erlotinib	85	12	1.170	0.731–1.871	0.513			
Gefitinib	32	15.8	0.894	0.507–1.577	0.699			
Icotinib	4	N/A	0.227	0.0229–2.247	0.205			
2nd generation EGFR TKI								
Afatinib	33	9.2	2.224	1.109–4.458	**0.024**			
Dacomitinib	4	6	1.318	0.155–11.237	0.801			
3rd generation EGFR TKI								
Osimertinib	121	16.8	0.720	0.455–1.141	0.162			
Zorifertinib	2	24	0.629	0.0750–5.282	0.67			
Furmonertinib	1	N/A	N/A	N/A	N/A			
EGFR TKI dosing regimens								
Osimertinib 80 mg daily	94	17.3	1.952	0.859–4.436	0.110			
Osimertinib 160 mg daily	13	11						
Chemotherapy for LM simultaneously to EGFR TKI								
No	208	15.3	0.733	0.411–1.307	0.292			
Yes	48	16.25						
Route of administration for chemotherapy concurrently to EGFR TKI								
Intravenous or oral only	17	16.25	1.027	0.431–2.446	0.952			
Intrathecal only	24	51.8	0.622	0.249–1.554	0.309			
Intrathecal and intravenous or oral	8	12.9	1.905	0.691–5.256	0.213			
Concurrent bevacizumab for LM								
No	251	14	0.623	0.327–1.188	0.151			
Yes	29	18						
Radiotherapy for LM								
No	203	15.3	0.738	0.449–1.212	0.230			
Yes	53	17						
Type of radiotherapy for LM								
Stereotactic radiosurgery	5	14.5	2.392	0.585–9.773	0.225			
Whole-brain radiotherapy	44	21	0.449	0.131–1.543	0.204			

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Table 3 (*continued*)

OVERALL SURVIVAL	Patient lines of therapy	Median OS (months)	Univariable Hazard Ratio	Univariable 95 % CI	Univariable P value	Adjusted Hazard Ratio	Multivariable 95 % CI	Adjusted P Value
Whole-brain radiotherapy and spinal radiotherapy	1	N/A	N/A	N/A	N/A			

NOTE. Univariate and multivariate hazard ratios, 95 % CIs, and P-values calculated with a multilevel mixed-effects logistic regression model with article as the random-effects variable. Bold values indicate $P < 0.05$. **Abbreviations:** CI, confidence interval; mOS, median overall survival; LM, leptomeningeal metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; IV.

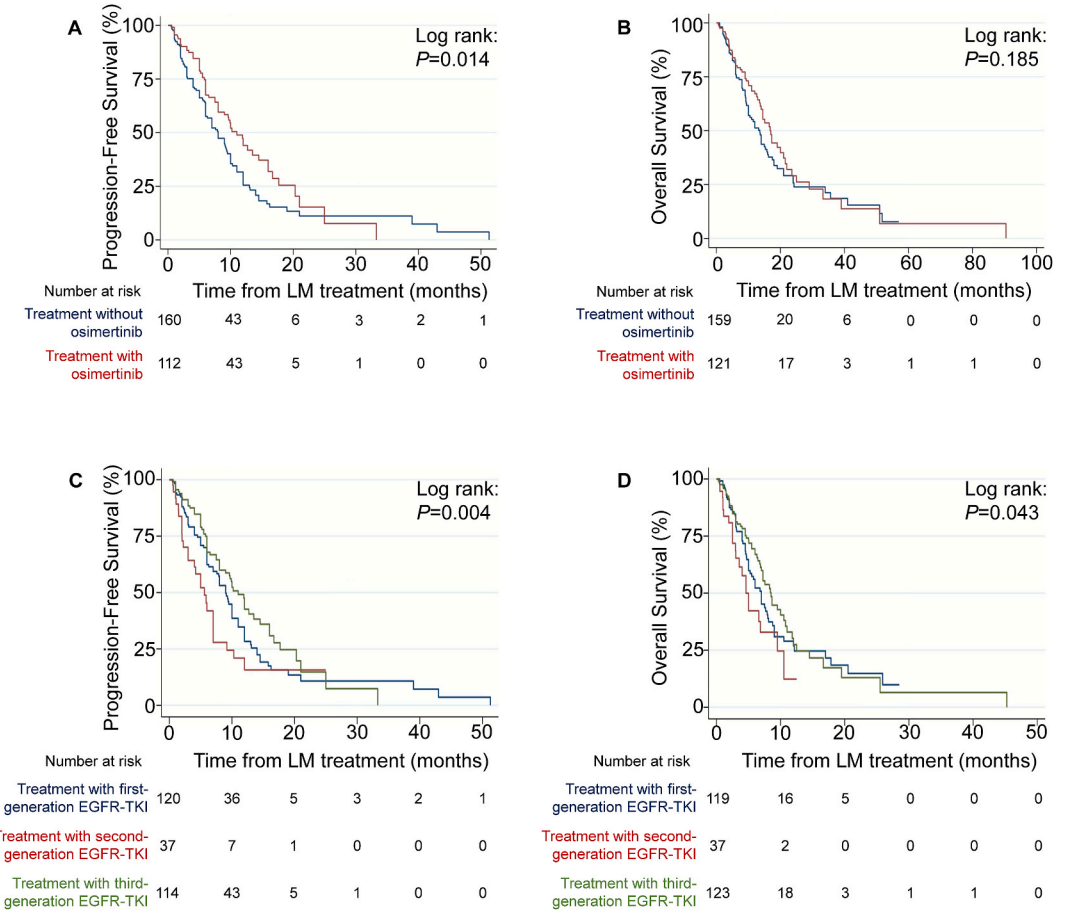

Fig. 2. Comparison of osimertinib to alternative EGFR-TKI. (A) CNS-specific PFS and (B) OS of patients who received osimertinib versus other EGFR-TKI. (C) CNS-specific PFS and (D) OS of patients who received first-generation versus second-generation versus third-generation EGFR-TKIs. **NOTE.** P-values calculated with Log-Rank test. **Abbreviations**: LM, leptomeningeal metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CNS, central nervous system; PFS, progression free survival; OS, overall survival.

Similarly, concurrent treatment with bevacizumab, as systemic therapy for *EGFR*-mutated NSCLC LM patients, was not associated with differential outcomes (PFS: HR = 0.71, 95 % CI: 0.38–1.32, $P = 0.27$; OS: HR = 0.62, 95 % CI: 0.33–1.19, $P = 0.15$) (Tables 2 and 3). Concurrent radiotherapy, either as WBRT or stereotactic radiosurgery, was also not associated with differential OS or CNS-specific PFS (PFS: HR = 0.88, 95 % CI: 0.58–1.33, $P = 0.54$; OS: HR = 0.74, 95 % CI: 0.45–1.21, $P = 0.23$) (Tables 2 and 3).

3.6. Quality assessment

This meta-analysis primarily included patients reported in retrospective studies, potentially introducing higher bias compared to those identified in prospective studies. Within our cohort, a significant difference in CNS-specific PFS was observed between patients

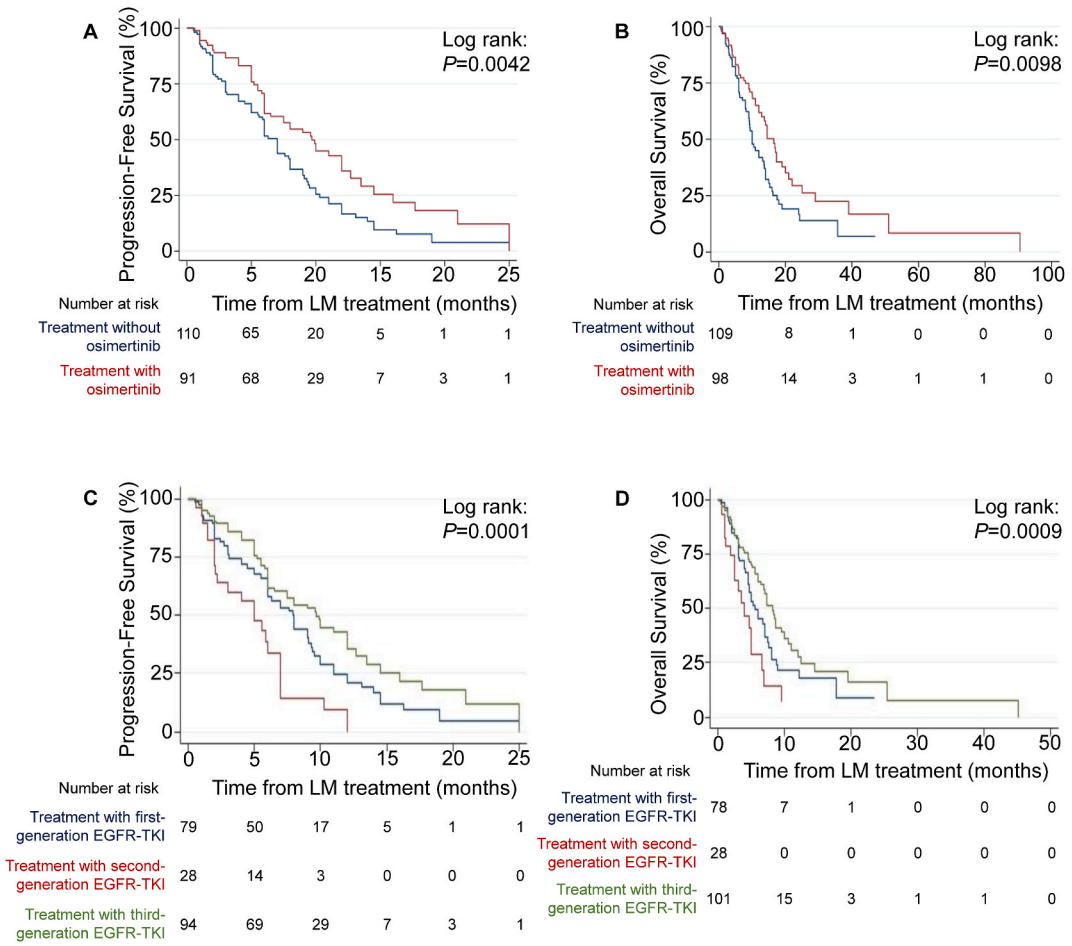

Fig. 3. Comparison of osimertinib to alternative EGFR-TKI in patients who received prior EGFR-TKI. Subgroup analysis of (A) CNS-specific PFS and (B) OS of osimertinib versus other EGFR-TKIs among patients who have previously received EGFR-TKIs. Subgroup analysis of (C) CNS-specific PFS and (D) OS of first-generation versus second-generation versus third-generation EGFR-TKIs among patients who have previously received EGFR-TKIs. **NOTE**. P-values calculated with Log-Rank test. **Abbreviations**: LM, leptomeningeal metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CNS, central nervous system; PFS, progression free survival; OS, overall survival.

identified from retrospective and prospective studies, while no difference was noted in OS (PFS: HR = 2.22, 95 % CI: 1.042–4.71, P = 0.039; OS: HR = 2.56, 95 % CI: 0.87–7.54, P = 0.089) (Tables 2 and 3). Moreover, studies with a high risk of bias (3 or less) showed no significant difference in CNS-specific PFS and OS compared to studies with a low risk of bias (4–5) (PFS: HR = 0.77, 95 % CI: 0.51–1.71, P = 0.23; OS: HR = 0.68, 95 % CI: 0.40–1.15, P = 0.15) (Tables 2 and 3).

4. Discussion

EGFR-TKIs have been used as standard of care for *EGFR*-mutated lung cancer patients with LM in the absence of published randomized controlled trial data for this patient population. We present the largest meta-analysis of EGFR-TKI-treated NSCLC LM patients to date, comprising 243 patients who received a total of 282 total lines of therapy extracted from 128 individual studies.

Third-generation EGFR-TKIs, notably osimertinib, have been developed with the goal of overcoming the on-target T790 M gatekeeper mutation associated with resistance to first- and second-generation EGFR-TKIs [158]. Osimertinib demonstrated a survival benefit compared to conventional chemotherapy when used as salvage therapy in *EGFR* T790M-positive NSCLC patients who had progressed on prior EGFR-TKI in the AURA3 trial [18]. The FLAURA trial subsequently demonstrated superior survival outcomes for osimertinib compared to first-generation gefitinib or erlotinib when used as first-line therapy for *EGFR*-mutated advanced NSCLC [20, 21].

Several prospective single-armed studies have demonstrated the potential clinical benefit of osimertinib in NSCLC patients with LM. The single-arm BLOOM study evaluated the efficacy of osimertinib in 41 EGFR-mutated NSCLC patients with LM that had progressed on a previous EGFR-TKI therapy. The patients in the study treated with osimertinib exhibited a mPFS of 8.6 months and a mOS of 11.0 months [159]. Furthermore, Park et al. demonstrated similar results in a phase II single-arm prospective study in lung cancer

LM patients treated with osimertinib, with a mOS of 13.3 months and mPFS of 8.0 months [160]. Furthermore, a meta-analysis of the AURA trials similarly revealed mOS of 18.8 months and mPFS of 11.1 in osimertinib-treated patients with stable *EGFR* T790M-mutated NSCLC LM [31]. As we were unable to extract individual patient data from these prospective studies, they were not included in our dataset (Appendix C).

In our dataset, patients treated with EGFR-TKIs of all generations exhibited a mOS of 14.5 months, similar to results reported in these previous studies [159–162]. We observed a significantly prolonged CNS-specific PFS and a non-significant trend towards a prolonged OS with osimertinib compared to all other EGFR-TKIs in our entire cohort. However, we observe that these differences are strongly dependent upon whether patients received prior EGFR-TKI therapy. Patients whose tumors were refractory to EGFR-TKIs derived significant benefit from osimertinib, while patients who were not previously treated with EGFR-TKI had similar outcomes regardless of whichever EGFR-TKI was used. This suggests that the survival benefit of osimertinib in our cohort is largely due to its ability to overcome resistance to earlier-generation EGFR-TKIs, rather than its reported enhanced CNS activity. In support of this finding, we describe significantly prolonged CNS-specific PFS for osimertinib compared to other EGFR-TKIs in LM patients with *EGFR* T790 M point mutations.

Furthermore, we observe that afatinib is associated with worse outcomes compared to other EGFR-TKIs. This finding is driven by patients who were previously treated with prior-generation EGFR-TKIs and that afatinib cannot overcome resistance to such EGFR-TKIs. Indeed, afatinib has been previously shown in the LUX-Lung 1 trial to confer no survival benefit compared to placebo in NSCLC patients who were pre-treated with first-generation EGFR-TKIs [163]. Thus, this lack of survival benefit is likely driven by the inability of afatinib to overcome resistance mechanisms to first-generation EGFR-TKIs, such as *EGFR* T790 M point mutations [164].

Our findings corroborate the results of other smaller cohort studies by Hong et al. and Tamura et al. who similarly did not observe an OS benefit with osimertinib compared to first- and second-generation EGFR-TKIs in patients with LM [165,166]. Together, this suggests that, in the context of LM, the survival benefit associated with osimertinib is limited to its ability to overcome resistance to earlier-generation EGFR-TKI, and not due to increased therapeutic activity in LM.

In preclinical models, osimertinib has demonstrated superior CNS activity compared to other EGFR-TKIs, as demonstrated by increased blood-brain barrier penetration [22,167]. These findings have been congruent with subgroup analyses of both the AURA3 and FLAURA trials; *EGFR*-mutated NSCLC patients with brain metastases similarly exhibited superior response rates and PFS for osimertinib employed in first- and second-line settings [23,168]. However, these lesions largely represent parenchymal brain metastases that were stable and/or locally treated at the time of patient enrollment. The data from these clinical trials contrasts substantially with the patients included in our dataset. Indeed, leptomeningeal metastases differ from parenchymal brain metastases in several ways. Notably, the blood-brain and blood-CSF barriers are distinct entities with both unique anatomical structures and expression profiles of efflux transporters, cellular permeabilities and interactions with cancer cells [1,2,169,170]. Moreover, the intrinsic biology underlying organotropism to the brain parenchyma and leptomeninges are divergent [2,171]. While dramatic differences in the efficacy of anti-cancer therapies between parenchymal and leptomeningeal metastases have not been observed in current literature, there is a lack of randomized prospective studies properly comparing treatment efficacies in parenchymal and leptomeningeal metastases.

The divergent biology between parenchymal brain metastases and LM can be further highlighted by their differing effective treatment modalities. Parenchymal brain metastases are amenable to local treatments, such as stereotactic or WBRT, which have demonstrated efficacy in parenchymal brain metastases but not LM [172]. In fact, although treatment guidelines for LM include WBRT, there is inconsistent evidence as to whether RT truly provides a significant survival benefit for patients with LM [8,173]. Retrospective studies evaluating the use of radiotherapy for LM in NSCLC patients did not identify a survival benefit, which is consistent with our findings [174,175]. Interestingly, specialized techniques, such as craniospinal irradiation, treating the entire CSF compartment is a treatment modality that has recently demonstrated clinical benefit in a phase II randomized controlled trial of LM patients [176,177].

A growing body of literature has described superior clinical outcomes with osimertinib compared to other EGFR-TKIs in NSCLC patients with *EGFR* exon 19 deletion mutations and CNS involvement, including LM [166,178]. Meanwhile, these clinical benefits were limited in patients with *EGFR* L858R point mutations [166,178,179]. Our findings are consistent with these findings, as we similarly describe prolonged survival for osimertinib compared to other EGFR-TKIs in LM patients with *EGFR* exon 19 deletion mutations, which was not observed in LM patients with *EGFR* L858R point mutations. These findings further highlight the role of identifying and classifying different *EGFR* mutational statuses to predict efficacy of specific EGFR-TKIs.

Several studies have attempted to combine additional therapeutic agents with EGFR-TKI for *EGFR*-mutated NSCLC. The addition of bevacizumab to EGFR-TKIs did not improve OS, data consistent with the results we report herein [180]. Early data from the FLAURA2 study demonstrated that chemotherapy, in addition to osimertinib, is superior to osimertinib alone for advanced NSCLC [181]. However, the findings described herein are not consistent with this observation. We hypothesize that this is because patients with CNS metastases do not derive much benefit from conventional chemotherapy due to the unique anatomy and microenvironment of the blood-brain and blood-CSF barriers that limit chemotherapy penetrance [2].

There are several novel EGFR-TKIs in development which may ultimately impact the care of patients with LM. Zorifertinib is a promising novel third-generation EGFR-TKI, which has shown excellent CNS penetration and antitumor activity in murine models [82,182,183]. An early phase trial conducted by Ahn et al. showed that zorifertinib exhibits CNS penetration in EGFR-mutated NSCLC patients with CNS metastases or LM [184]. Early results from a phase III trial have shown significantly superior mPFS and objective response rates for zorifertinib compared to first-generation EGFR-TKIs in EGFR-mutated NSCLC patients with CNS metastases [185]. In the osimertinib refractory setting, the EGFR-TKI lazertinib and the bispecific EGFR-MET antibody amivantamab has demonstrated encouraging data thus far. Lazertinib is an irreversible third-generation EGFR-TKI with high selectivity for primary and *EGFR* T790 M mutation [186]. In murine models, lazertinib demonstrated excellent CNS penetration and comparable anti-tumor efficacy to

osimertinib, along with decreased toxicity [187]. In the LASER301 phase III clinical trial, lazertinib demonstrated prolonged mPFS compared to gefitinib as first-line treatment in *EGFR*-mutated NSCLC patients both with and without CNS metastases [188]. Amivantamab is a human bispecific antibody targeting *EGFR* exon 20 insertions [189]. The PAPILLON phase III clinical trial compared amivantamab plus chemotherapy versus chemotherapy alone in advanced NSCLC patients with primary *EGFR* exon 20 insertion mutations [190]. Amivantamab plus chemotherapy resulted in prolonged mPFS compared to chemotherapy alone in NSCLC patients both with and without brain metastases. Further investigations comparing the survival benefits of these novel therapies, osimertinib and previous-generation EGFR-TKIs among NSCLC patients with LM are warranted.

Several limitations are associated with our study. Firstly, many patients included were derived from case reports and retrospective case series, potentially introducing selection biases that could inflate survival estimates beyond real-world expectations. Regarding publications from which data couldn't be collected, the challenge lay in the presentation of mOS and mPFS for entire patient cohorts, making it impossible to obtain individualized patient data for analysis. Despite repeated requests to the authors for individualized patient data, no responses were received, further limiting data availability for analysis. Another potential source of methodological bias is the restriction of our database search to English titles and abstracts. Given the higher incidence of EGFR-mutated NSCLC in East Asian countries such as China, South Korea, Japan, and others, studies published in languages other than English from these regions might have been overlooked in our meta-analysis [191]. This could potentially lead to an incomplete representation of available data and affect the generalizability of our findings. While efforts were made to mitigate these biases, including quality assessment, second reviewer extraction for a subset of abstracts, and translation of non-English articles retrieved in our database search, a randomized controlled trial would offer the most suitable approach to directly compare the efficacy of EGFR-TKIs in treating LM. However, as of now, no such studies have been conducted.

This meta-analysis describes the largest cohort of *EGFR*-mutated NSCLC LM patients treated with EGFR-TKIs compiled to date. Our findings suggest that survival benefits are comparable for first-, second-, and third-generation EGFR-TKIs in the treatment of EGFR-TKI naïve *EGFR*-mutated NSCLC LM patients. These findings may potentially have clinical implications especially in resource-limited settings, wherein osimertinib may not be available or is cost-ineffective compared to off-patent medications. However, osimertinib demonstrates a survival benefit in LM patients harboring primary *EGFR* exon 19 deletion mutations, acquired *EGFR* T790 M point mutations, and experiencing disease progression on previous-generation EGFR-TKI therapy. Concurrent administration of non-EGFR-TKI therapies, such as chemotherapy and other targeted therapies (e.g. bevacizumab), does not confer a survival benefit in this patient population, suggesting that, in the absence of new data, there is no role for these agents outside of a highly treatment refractory setting or clinical trial. Overall, our study serves as an important resource for informing clinical practice in managing lung cancer patients with LM and highlights the need for prospective studies targeting this challenging-to-treat patient population.

Data availability statement

Data available upon request.

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none.

Registration

This study is registered on PROSPERO (ID: CRD42021292539).

CRediT authorship contribution statement

David J.H. Bian: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Anna-Maria Lazaratos:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Sarah M. Maritan:** Writing – review & editing, Investigation. **Andrea Quaiattini:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Zhimin Zeng:** Writing – review & editing, Investigation. **Zhengfei Zhu:** Writing – review & editing, Investigation. **Ugur Sener:** Writing – review & editing, Investigation. **Rachna Malani:** Writing – review & editing, Investigation. **Yu Jung Kim:** Writing – review & editing, Investigation. **Eiki Ichihara:** Writing – review & editing, Investigation. **Victor Cohen:** Writing – review & editing, Writing – original draft. **April A.N. Rose:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Nathaniel Bouganim:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Matthew Dankner:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:April A. N. Rose conflicts of interest:

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Appendix A. Supplementary data

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