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REVIEW

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

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ABSTRACT

Introduction: Nearly 60% of patients with non-small cell lung cancer (NSCLC) present with metastatic disease, and approximately 20% have brain metastases (BrMs) at diagnosis. During the disease course, 25–50% of patients will develop BrMs. Despite available treatments, survival rates for patients with NSCLC and BrMs remain low, and their overall prognosis is poor. Even with newer agents for NSCLC, options for treating BrMs can be limited by their ineffective transport across the blood–brain barrier (BBB) and the unique brain tumor microenvironment. The presence of actionable genomic alterations (AGAs) is a key determinant of optimal treatment selection, which aims to maximize responses and minimize toxicities. The objective of this systematic literature review (SLR) was to understand the current landscape of the clinical management of patients with NSCLC and BrMs, particularly those with AGAs.

Method: A Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-compliant SLR was conducted to identify studies in patients with BrMs in NSCLC. Searches used the EMBASE and MEDLINE® databases, and articles published between January 1, 2017 and September 26, 2022 were reviewed.

Results: Overall, 179 studies were included in the SLR. This subset review focused on 80 studies that included patients with NSCLC, BrMs, and AGAs (19 randomized controlled trials [RCTs], two single-arm studies, and 59 observational studies). Sixty-four of the 80 studies reported on epidermal growth factor receptor (*EGFR*) mutations, 14 on anaplastic lymphoma kinase (*ALK*) alterations, and two on both alterations. Ninety-five percent of studies evaluated targeted therapy. All RCTs allowed patients with previously treated, asymptomatic, or neurologically stable BrMs; the percentage of asymptomatic BrMs varied across observational studies.

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Conclusions: Although targeted therapies demonstrate systemic benefits for patients with NSCLC, BrMs, and AGAs, there remains a continued need for effective therapies to treat and prevent BrMs in this population. Increased BBB permeability of emerging therapies may improve outcomes for this population.

Keywords: NSCLC; Brain metastases; Systematic literature review; *EGFR* mutation

Key Summary Points

More than half of newly diagnosed patients with lung cancer have advanced or metastatic disease, 10–26% present with brain metastases at the time of diagnosis, and another 30% will develop brain metastases over the course of their disease.

Current treatment options, particularly in later lines of therapy, are limited in their ability to pass through the blood–brain barrier, leaving a continuing treatment need in patients with non-small cell lung cancer (NSCLC) who have or develop brain metastases.

This study reviewed the current global landscape of clinical management used for patients with NSCLC, brain metastases, and actionable genomic alterations to gain a better understanding of treatment needs and how emerging therapies can fill those gaps.

For patients with NSCLC, brain metastases, and actionable genomic alterations, the current standard of care is suboptimal, and even with targeted therapies and local therapies (e.g., radiotherapies), prognosis is generally poor, regardless of the therapeutic regimen.

These findings emphasize the need for new therapies and therapeutic approaches that can improve clinical outcomes for this patient population.

INTRODUCTION

Lung cancer is the most common cause of cancer mortality worldwide, with an estimated 1.80 million deaths annually [1]. Non-small cell lung cancer (NSCLC) accounts for 81% of all lung cancers [2]. More than half of newly diagnosed patients with lung cancer have advanced or metastatic disease [3]; 10–26% present with brain metastases at diagnosis, and another 30% will develop brain metastases over the course of their disease [4–6]. Although various treatments are available, including surgery, stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT), systemic therapy, and supportive care, survival rates for patients with NSCLC and brain metastases remain low, with overall poor patient outcomes and prognosis [7].

In the past, treatment strategies had been based primarily on the stage of disease or histologic appearance (squamous vs. non-squamous). Now, in addition to staging and histology, an improved understanding of tumor biology, along with overall advancements in treatment for NSCLC, has facilitated personalization of clinical management. Research has demonstrated that the presence or absence of actionable genomic alterations (AGAs), e.g., alterations in *EGFR*, *ALK*, *ROS1*, and other less common alterations, is a key determinant of optimal treatment selection, which aims to maximize responses and minimize toxicities [8]. To test for AGAs, advanced polymerase chain reaction (PCR)-based methods, such as quantitative PCR (qPCR) and reverse transcriptase PCR (RT-PCR), are used. Since brain metastases genetically diverge from the main tumor in NSCLC, evaluating for AGAs is important to determine therapy. Circulating tumor DNA (ctDNA) from cerebrospinal fluid seems to provide a better representation of brain metastases profiling compared to plasma ctDNA [9]. Tissue sampling of brain metastases poses a particular challenge, as many patients are not candidates for brain resections or have tumors in inaccessible sites. The low availability of tissue samples makes designing comprehensive studies problematic [10]. Still, AGAs that predict response to

targeted treatment, including tyrosine kinase inhibitors (TKIs), are only present in approximately 30% of patients with NSCLC [8]. Even with recent advancements in earlier-line treatment, e.g., third-generation epidermal growth factor receptor (EGFR) TKIs, patients with both NSCLC and brain metastases have limited therapeutic options in later lines as many current treatments are unlikely to cross the blood–brain barrier (BBB) because of their molecular size [11].

In addition, patients often develop resistance to treatments, and therapeutic options may be associated with adverse events due to off-target drug activity [12]. For the development of new therapeutic options, such as fourth-generation EGFR TKIs and antibody–drug conjugates (ADCs), it will be important to understand their comparative activity in relation to the current treatments used for patients with NSCLC and brain metastases.

While the overall objective of the systematic literature review (SLR) was to understand the current landscape of clinical characteristics and clinical management for patients with brain metastases in NSCLC, this current review focused on summarizing the subset of studies with patients whose NSCLC harbored AGAs (e.g., *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET*, *RET*, *KRAS*, *HER2*).

METHODS

An SLR was performed following standard methods outlined in the updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 and Cochrane guidelines [13, 14]. This article is based on previously published scientific studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

The criteria are presented according to the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Study design) format (Table 1). The inclusion and exclusion criteria are presented in Table 2.

Table 1 PICOTS eligibility criteria for overall systematic literature review

Criterion	Description
Population	Adults with brain metastases in NSCLC within the following patient populations
	With actionable genomic alterations
	EGFR, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET*, *RET*, *KRAS*, *HER2*
	Without actionable genomic alterations
Intervention	Any pharmacotherapy, radiotherapy, or surgery
Comparators	Any standard-of-care or emerging therapy
Outcomes	Clinical characteristics: signs, symptoms, and pathology in stable and active disease
	Clinical management: current methodologies of treatment, limitations, evolution of brain metastases post-treatment (including radiotherapy)
	Unmet needs: frequency of response & non-response, intracranial efficacy or lack thereof, reasons for non-response with standard of care
	Emerging therapies: clinical activity on brain metastases, bioavailability, trends for emerging agents, or regimens specifically addressing brain metastases
Date range	January 1, 2017 to September 26, 2022 (search date)
Study design	Phase 3 or 4 clinical trials (50 or more participants)
	Observational/real-world studies (100 or more participants)
	Clinical practice guidelines or preferred practice patterns
Other	Limited to English language only
	No geographical limit
	Excluded conference abstracts

Table 2 Eligibility criteria amendments

Areas targeted for scope refinement and prioritization	Original protocol	Protocol amendment after title and abstract screening	Protocol amendment after full-text screening
Time restriction	Last 5 years	Limit to January 1, 2017 to September 26, 2022	Limit to January 1, 2017 to September 26, 2022
Sample size	–	Exclude studies with ≤ 50 patients	Include RCTs with ≥ 50 patients
			Include observational studies with ≥ 100 patients
Publication type	–	–	Include only full-text articles; exclude conference abstracts
Study type	–	–	Include only phase 3/4 trials; exclude phase 1/2 trials

RCT randomized controlled trial

During the course of the SLR, amendments were made (December 5, 2022) to the protocol to refine the eligibility criteria and focus on the most relevant and robust information available. All amendments were made prior to the data extraction phase and were applied universally across all records (Table 2).

Databases Searched

The search was conducted in the following databases using the OvidSP® platform:

- EMBASE
- MEDLINE® Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Medline® Daily, Medline and Versions®

The search strategy was based on a combination of free-text words, indexing terms (e.g., Excerpta Medica database [EMBASE] subject heading [EMTREE] or Medical Subject Headings [MESH] terms) and their relationship using Boolean terms (e.g., and, or, not). Full strategies (including search dates) for all sources searched are included in Tables S1 and S2.

Screening Process

Publications identified through the systematic literature search were evaluated in a stepwise process to assess whether they should be included for data extraction.

Step 1—Title and abstract review: All unique records identified from the searches were reviewed on the basis of the predefined PICOTS criteria described in Table 1. Two reviewers independently screened titles and abstracts and classified each record as either (1) exclude or (2) continue to full-text review. Any discrepancy between reviewers was resolved by a third reviewer, who also confirmed the classifications for all studies marked for full-text review and from a sample of excluded abstracts. Furthermore, artificial intelligence technology was used to screen all excluded records and assign each a probability of likelihood for inclusion. Any study with a probability ranking over 85% was rescreened.

On the basis of the large number of potentially relevant studies identified after title and abstract screening (> 800), the eligibility criteria were amended to prioritize the most relevant and applicable evidence available that would address the research questions of interest. The amendments made following title and abstract screening are shown in Table 2.

Step 2—Full-text review: Full-texts of publications included after title and abstract review, and meeting the amended eligibility criteria, were screened by two reviewers on the basis of

the amended PICOTS criteria. A third reviewer resolved any discrepancies.

Following full-text screening, additional amendments were made to better refine the project scope and identify the most relevant studies. The amendments made following full-text screening are shown in Table 2. Studies that met the amended PICOTS criteria after full-text review were included in the SLR.

Records that were excluded after review of the full-text report were documented, along with a clear justification for their exclusion. All references included after completion of the full-text review were retained for quality assessment and data extraction.

Data Extraction

Extraction of data from the included studies was conducted using a standardized Excel-based data extraction template. For each included study and methodological characteristics, selection criteria, study population/patient characteristics, and results were collected. If results for the same study were reported in more than one publication, the relevant records were grouped per study. Data extraction from included sources was conducted by two investigators independently, with discrepancies resolved by a third reviewer.

Quality Assessment

The quality assessment analyzes the strength and robustness of the available evidence with the aim of evaluating the applicability and internal and external validity of studies.

A quality assessment of individual papers was performed according to the study design. The Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) [15] was used for randomized controlled trials (RCTs), and the Newcastle–Ottawa Scale (NOS) [16] was used for non-randomized studies. The quality assessment results were recorded in a tabular format in the data extraction file. The quality assessment for studies included in this NSCLC, brain metastases, and AGA subgroup analysis are available in Tables S4 and S5.

Supplemental Search Results

Although not eligible for inclusion in the SLR, the most recent meetings of five conferences (Table S6) and two major clinical trial registries were searched to provide a current view of the evidence landscape (see supplementary materials).

RESULTS

The search and screening process in the SLR is reported in accordance with the PRISMA flow diagram (Fig. 1).

Overall Systematic Search Output

The database and registry searches identified a total of 7884 records. Following deduplication, 3815 records underwent title and abstract screening, of which 901 records were classified as potentially relevant according to the original PICOTS criteria. After the PICOTS criteria were amended, 394 records were excluded and not sought for full-text review; the full texts of the remaining 507 records were retrieved and reviewed.

After full-text review and amendments to the PICOTS criteria, 432 records were excluded, and 75 records meeting the eligibility criteria were included. An additional 150 records were identified for inclusion, as were an additional 12 records identified from reviewing bibliographies of relevant review articles, based on a concurrent SLR on overall unmet needs in NSCLC with similar eligibility criteria. Overall, 237 publications reporting data on 179 studies were included in the review. The 179 studies included 33 RCTs, two single-arm trials, and 144 observational studies. Most RCTs (n = 17, 52%) were multiregional, whereas most observational studies (n = 75, 52%) were conducted in Asia.

Studies were further characterized as follows:

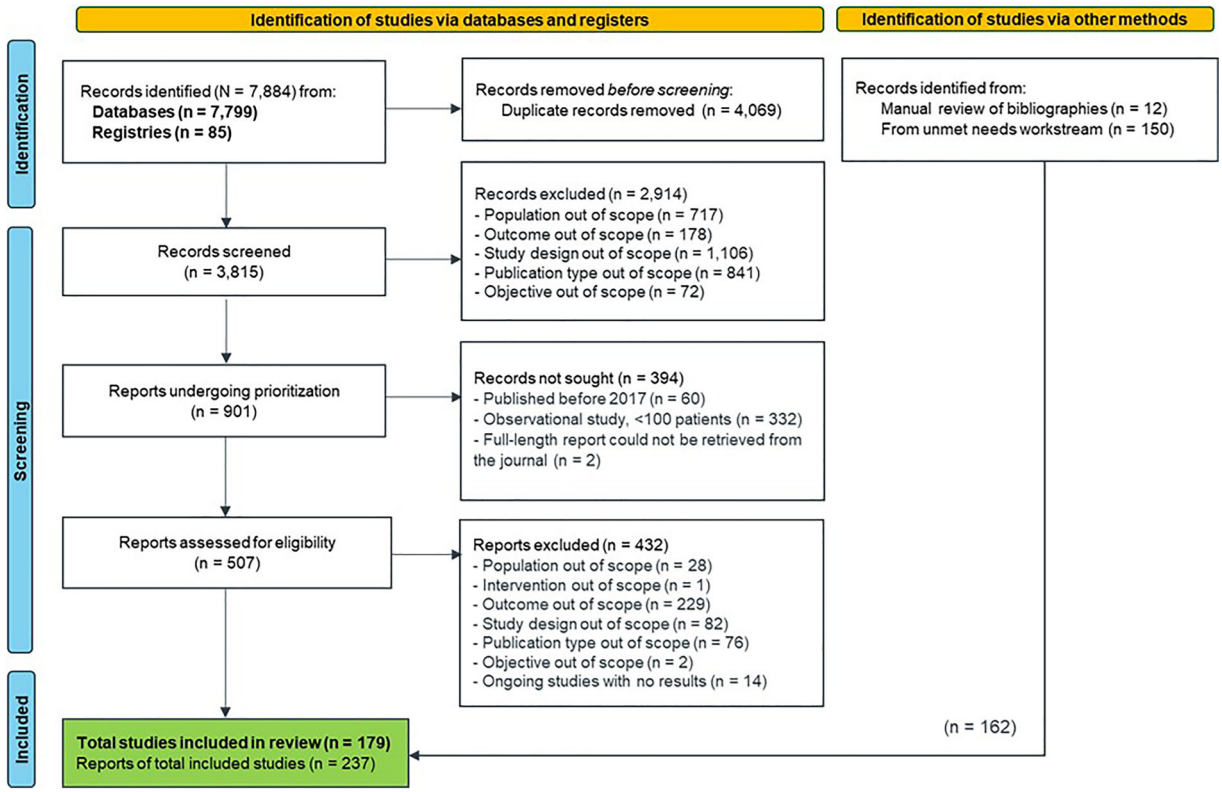

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of literature search results. Figure shows the flow of the study identification and selection process. In total, 7884 records were originally identified. After removal of duplicates, 3815 records were screened. Several records were excluded throughout the process for reasons such as the population being out of scope, not having results because of an ongoing study, or the study design being out of scope. Ultimately, 179 studies were included in this review

Studies of patients with AGAs: Of the 80 studies that included patients with AGAs, 19 were RCTs, two were single-arm trials, and 59 were observational studies. These studies are summarized in Tables 3 and S3 [17–98].

Studies of patients without AGAs: Of the 18 studies of patients with no actionable mutations, nine were RCTs and nine were observational studies.

Studies of patients with or without AGAs: Of the 51 studies of patients with or without actionable mutations, five were RCTs and 46 were observational studies.

Studies of patients with not specified/unknown alterations: All 30 studies of patients with mutation status not specified or unknown were observational studies.

Results for Studies of Subgroup of Patients with NSCLC, Brain Metastases, and AGAs

Of the 19 RCTs, 10 were multiregional and nine were conducted in Asia (China, Japan, South Korea, Hong Kong, Malaysia, Taiwan, and Thailand). Only three trials enrolled fewer than 200 participants, 15 enrolled 200–500 participants, and one enrolled more than 500 participants (median 296 patients; range 119–556 patients). In the four RCTs reporting age and sex for the brain metastasis population, median age was 58.5 years (range 56–63), and median percentage of female patients was 60.5% (range 54–62%).

Of the two single-arm trials, one was multiregional and included 479 participants with *EGFR* mutations treated with targeted therapy

Table 3 Summary of studies for subgroup of patients with NSCLC, brain metastases, and actionable genomic alterations

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Addeo et al. 2021 [17]	Multinational	OBS	896	332 (37.1)	*EGFR*	1L	1G or 2G EGFR TKI	332	–	–	–
Bai et al. 2017 [18]	China	OBS	148	148 (100)	*EGFR*	2L	GEF	–	47 (31.8)	–	33 (34.7)
							ERL	–		–	21 (39.6)
Baldacci et al. 2022 [19]	France	OBS	208	160 (76.9)	*ALK*	2L +	LOR	160	–	–	–
Bilgin et al. 2021 [20]	Turkey	OBS	283	68(24.0)	*EGFR*	1L	AFA	21	–	–	–
							ERL or GEF	47	–	–	–
Bozorgmehr et al. 2021 [21]	Germany	OBS	401	102 (25.4)	*EGFR*	1L to > 3L	EGFR TKI, CT, palliative RT, de novo stage IV	89	–	–	–
							EGFR TKI, CT, palliative RT, secondary stage IV	13	–	–	–
Camidge et al. 2018 [22]	Intercontinental	RCT	275	81 (29.4)	*ALK*	1L	Brigatinib	40	–	24	31 (65.6)
							CRIZ	41	–	5.6	7 (14.0)
Chang et al. 2021 [23]	Taiwan	OBS	205	67 (32.7)	*EGFR*	1L	EGFR TKI (GEF, ERL, AFA)	67	–	–	–
Chen et al. 2020 [24]	China	OBS	148	148 (100)	*EGFR*	1L to 2L	EGFR TKI only	72	–	10.2	–
							EGFR TKI + WBRT	76	–	11.9	–
Chen et al. 2019a [25]	Taiwan	OBS	134	134 (100)	*EGFR*	1L	GEF	62	–	23.6	33 (53.2)
							ERL	49	–	27.8	34 (69.4)
							AFA	23	–	17.2	15 (65.2)
Chen et al. 2019b [26]	Taiwan	OBS	141	141 (100)	*EGFR*	1L +	EGFR TKI + WBRT	94	–	–	–
							EGFR TKI alone	47			
Chen et al. 2018 [27]	China	OBS	105	39 (37.1)	*EGFR*	1L or 2L	EGFR TKIs alone	39	9 (23.1)	6.8	26 (66.7)
							EGFR TKIs + concurrent WBRT	34	8 (23.5)	12.4	29 (85.3)
							WBRT followed by EGFR TKIs	32	8 (25.0)	9.1	24 (75.0)

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Chiu et al. 2022 [28]	Taiwan	OBS	310	137 (44.2)	*EGFR*	1L	EGFR TKI (GEF or ERL) ± BEV	137	–	–	–
de Marinis et al. 2021 [29]	Intercontinental	SA	479	83 (17.3)	*EGFR*	1L +	AFA	83	–	–	–
Doherty et al. 2017 [30]	Canada	OBS	184	184 (100)	*EGFR*/ *ALK*	1L	WBRT + SRS + TKIs	120	58 (48.3)	50.5	–
							SRS + TKIs	37	31 (83.8)	12	
							TKIs	27	24 (88.9)	15	
Duruisseaux et al. 2017 [31]	France	OBS	318	111 (34.9)	*ALK*	1L +	CRIZ	111	–	–	–
El Shafie et al. 2021 [32]	Germany	OBS	141	141 (100)	*EGFR*: 76.6% *ALK*: 23.4%	1L +	Delayed local therapy	54	45 (88.2)	10.6	–
							Early local therapy	87	41 (48.8)	19.4	–
Gijtenbeek et al. 2020 [33]	Netherlands	OBS	873	112 (12.8)	*EGFR*	1L	ERL	65	–	–	–
							GEF	29			
							AFA	18			
He et al. 2019 [34]	China	OBS	104	104 (100)	*EGFR*	1L	EGFR TKI (GEF, ERL, ICO) + WBRT	56	27 (48.2)	17.7	–
							EGFR TKI (GEF, ERL, ICO)	48	29 (60.4)	11	–
Horn et al. 2021 [35]	Intercontinental	RCT	290	90 (31.0)	*ALK*	1L	Ensartinib	40	40 (100)	–	–
							CRIZ	50	50 (100)	–	–
Huang et al. 2021 [36]	Taiwan	OBS	612	211 (34.4)	*EGFR*	1L +	GEF/ERL	113	–	–	–
							AFA	98			
Huang et al. 2022 [37]	Taiwan	OBS	516	151 (30.3)	*EGFR*	1L	AFA	151	–	–	–

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Hyun et al. 2020 [38]	South Korea	OBS	173	173 (100)	*EGFR*	–	EGFR TKI (GEF, ERL, AFA)	107	98 (91.6)	10.4	67 (62.6)
							WBRT followed by EGFR TKI (GEF, ERL, AFA)	36	22 (61.1)	10.8	26 (72.2)
							SRS followed by EGFR TKI (GEF, ERL, AFA)	30	21 (70.0)	15.8	18 (60.0)
Ito et al. 2021 [39]	Japan	OBS	160	160 (100)	*EGFR*	1L	AFA	75	–	–	–
							OSI	85			
Jahanzeb et al. 2020 [40]	USA	OBS	581	160 (27.5)	*ALK*	1L and 2L	ALK TKIs (CRIZ, CER, ALEC, BRIG)	160	–	–	–
Jia et al. 2019 [41]	China	OBS	114	114 (100)	*EGFR*	1L	SRS + EGFR TKI (GEF, ERL)	57	9 (15.8)	12.2	–
							WBRT + EGFR TKI (GEF, ERL)	57	5 (8.8)	11.5	–
Jiang et al. 2019 [42]	China	OBS	208	208 (100)	*EGFR*	1L	EGFR TKI (GEF, ERL, ICO) + BEV	59	38 (64.4)	14	39 (66.1)
							EGFR TKI (GEF, ERL, ICO)	149	95 (63.8)	8.2	62 (41.6)
Jung et al. 2020 [43]	South Korea	OBS	559	198 (35.4)	*EGFR*	1L	GEF	68	–	–	22 (64.7)
							ERL	58	–	–	15 (68.2)
							AFA	72	–	–	27 (72.9)
Jung et al. 2022 [44]	South Korea	OBS	737	287 (38.9)	*EGFR*	1L and 2L	1L AFA + 2L OSI	54	42 (77.8)	–	71 (24.7)
							1L AFA + 2L CT or other treatments	61	40 (65.6)		
							1L AFA + 2L systemic treatment or SC	46	37 (80.4)		
							1L AFA only	126	96 (76.2)		

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Ko et al. 2022 [45]	Taiwan	OBS	400	140 (35.0)	*EGFR*	1L	GEF or ERL or AFA ± denosumab	140	–	–	–
Kong et al. 2021 [46]	USA	OBS	502	222 (100)	*EGFR*	–	EGFR TKI (AFA, ERL, GEF)	222	–	–	–
Lee et al. 2021 [47]	South Korea	OBS	422	168 (39.8)	*EGFR*	1L to 2L	AFA	168	–	–	–
Lee et al. 2019a [48]	Taiwan	OBS	100	100 (100)	*EGFR*	1L +	EGFR TKI + brain surgery + WBRT	40	6 (15.0)	–	–
							EGFR TKI + WBRT	60	16 (26.7)	–	–
Lee et al. 2019b [49]	Taiwan	OBS	198	198 (100)	*EGFR*	–	WBRT	75	–	–	–
							SRS	21			
							Delayed radiation	27			
							Never cranial irradiation	75			
Lee et al. 2020 [50]	South Korea	OBS	351	351 (100)	*EGFR*	–	With or without OSI	351	–	–	–
Li et al. 2017 [51]	China	OBS	104	104 (100)	*EGFR*	–	EGFR TKI (GEF or ERL) or EGFR TKI (GEF or ERL) + WBRT	104	–	–	–
Li et al. 2019 [52]	China	OBS	195	195 (100)	*EGFR*	1L	WBRT followed by EGFR TKI (GEF, ERL, ICO)	67	51 (76.1)	–	–
							EGFR TKI (GEF, ERL, ICO) + WBRT	64	40 (68.8)	–	–
							EGFR TKI (GEF, ERL, ICO) followed by WBRT	64	46 (71.8)	–	–
Lin et al. 2019 [53]	Taiwan	OBS	125	125 (100)	*EGFR*	1L	GEF	28	–	–	–
							ERL	54	–	–	–
							AFA	43	–	–	–

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Liu et al. 2017 [54]	China	OBS	11	113 (100)	*EGFR*	1L to 2L	EGFR TKI (GEF, ERL, ICO) + early RT (WBRT, SRS)	49	10 (20.4)	21.4	–
							EGFR TKI (GEF, ERL, ICO)	37	32 (86.4)	24.4	–
							EGFR TKI (GEF, ERL, ICO) + salvage RT (WBRT, SRS)	27	18 (66.7)	23.6	–
Liu et al. 2020 [55]	USA	OBS	365	145 (39.7)	*EGFR*	1L to > 4L	OSI	124	–	–	–
							OSI + ASA	21	–	–	–
Lu et al. 2022a [56]	China	RCT	429	115 (26.8)	*EGFR*	1L	Aumolertinib	56	–	–	–
							GEF	59	–	–	–
Lu et al. 2022b [57]	China	RCT	444	160 (36.0)	*EGFR*	2L and 3L	Sintilimab + IBI305 + CT	53	53 (100)	–	–
							Sintilimab + CT	52	52 (100)	–	–
							CT alone	55	55 (100)	–	–
Magnuson et al. 2017 [58]	USA	OBS	351	351 (100)	*EGFR*	1L	ERL followed by WBRT or SRS	131	115 (87.7)	17	–
							WBRT followed by ERL	120	69 (57.5)	24	–
							SRS followed by ERL	100	51 (51.0)	23	–
Masuda et al. 2018 [59]	Japan	OBS	496	496 (100)	*ALK*	1L +	ALEC	496	–	–	–
Mehlman et al. 2019 [60]	France	OBS	226	121 (53.5)	*EGFR*	1L and > 2L	OSI (≥ 2L with T790M)	92	–	–	–
							OSI (≥ 2L without T790M)	26			
							OSI (1L)	3			
Miyawaki et al. 2019 [61]	Japan	OBS	176	176 (100)	*EGFR*	1L	EGFR TKI	107	97 (90.6)	12	–
							Local therapy	69	42 (60.9)	22	–

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Mok et al. 2017 [62]	Intercontinental	RCT	419	144 (34.4)	*EGFR* T790M	2L	OSI	93	93 (100)	–	–
Wu 2017 [63]				*n* with CNS metastases			PBC + PEM	51	51 (100)		
				116 (27.7)			OSI	75	–	11.7	30 (40.0)
				n with CNS lesions on BL brain scan (BICNR)			PBC + PEM	41		5.6	7 (17.1)
Nadler et al. 2020 [64]	USA	OBS	402	201 (50.0)	*EGFR*	1L +	ERL	201	–	–	–
Patel et al. 2017 [65]	USA	OBS	189	78 (41.3)	*EGFR*	1L +	ERL	78	–	–	–
Peters et al. 2017 [66]	Intercontinental	RCT	303	122 (40.3)	*ALK*	1L	ALEC	64	–	–	–
							CRIZ	58	–	–	–
Ramotar et al. 2020 [67]	Canada	OBS	198	198 (100)	*EGFR*	1L	SRS	43	–	–	–
							WBRT	121			
							TKI	34			
Saida et al. 2019 [68]	Japan	OBS	104	104 (100)	*EGFR*	1L	EGFR TKI without upfront brain RT	65	55 (84.6)	11.1	24 (36.9)
							EGFR TKI with upfront brain RT	39	19 (48.7)	15.6	14 (35.6)
Saito et al. 2019 [69]	Japan	RCT	228	72 (31.6)	*EGFR*	1L	ERL + BEV	36	36 (100)	–	–
							ERL	36	36 (100)	–	–
Shaw et al. 2017 [70]	Intercontinental	RCT	231	134 (58.0)	*ALK*	2L/2L +	CER	65	–	–	–
							CT	69	–	–	–
Shaw et al. 2020 [71]	Intercontinental	RCT	296	78 (26.4)	*ALK*	1L	LOR	38	–	–	23 (60.5)
							CRIZ	40	–		6 (15.0)

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Shi et al. 2017 [72]	China	RCT	296	81 (27.3)	*EGFR*	1L	ICO	41	–	–	–
							CT	40	–	–	–
Shi et al. 2022 [73]	China	RCT	358	127 (35.4)	*EGFR*	1L	Furmonertinib	65	–	20.8	–
							GEF	62	–	9.8	–
Solomon et al. 2018 [74]	Intercontinental	RCT	343	92 (26.8)	*ALK*	1L	CRIZ	45	–	–	–
							CT	47	–	–	–
Soria et al. 2017 [75]	Intercontinental	RCT	376	121 (32.2)	*ALK*	1L	CER	59	–	–	25 (46.3)
							PBC	62	–	–	11 (21.2)
Soria et al. 2018 [76] and Reungwetwattana et al. 2018 [77]	Intercontinental	RCT	556	116 (21.0)	*EGFR*	1L	OSI	53	–	–	40 (65.6)
							GEF or ERL	63	–	–	29 (43.3)
Tang et al. 2021 [78]	China	OBS	351	132 (37.6)	*EGFR* T790M	–	OSI	132	–	–	–
Teocharoen et al. 2021 [79]	Thailand	OBS	304	149 (49.0)	*EGFR*	1L to > 2L	EGFR TKI	149	–	–	–
Tu et al. 2022 [80]	Asia	SA	541	103 (19.0)	*EGFR*	1L to 3L +	AFA	103	103 (100)	–	–
Wang et al. 2018 [81]	China	OBS	181	181 (100)	*EGFR*	1L to > 2L	Asymptomatic pts EGFR TKI ± RT (WBRT, SRS)	132	132 (72.9)	iPFS in 181 pts B/C RT *n* = 91: 11.7	B/C RT *n* = 91:51 (55.6)
							Symptomatic pts EGFR TKI ± RT (WBRT, SRS)	49		Upfront RT *n* = 90: 9.7	Upfront RT *n* = 90: 56 (62.6)

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Wang et al. 2020 [82]	China	OBS	113	113 (100)	*EGFR*	–	None	18	67 (59.3)	–	
							RT (WBRT, SRS)	27		12	
							EGFR TKIs in TKI-naïve	14		7	
							CT	15		10	
							EGFR TKIs + RT (WBRT, SRS)	39		21	
Wolf et al. 2022 [83]	Intercontinental	RCT	119	76 (63.9)	*ALK*	3L	ALEC	50	–	9.6	–
							PEM or DOC	26	–	1.4	–
Wu et al. 2018 [84]	Intercontinental	RCT	207	53 (25.6)	*ALK*	1L	CRIZ	21	–	NR	–
							CT	32	–	16	–
Yang et al. 2017a [85]	China	OBS	228	228 (100)	*EGFR*	–	BEV + GEF + WBRT	77	–	–	–
							WBRT	75			
Yang et al. 2017b [86]	China	RCT	176	176 (100)	*EGFR*	1L to 2L	ICO	85	–	10	–
							WBRT ± CT	91	–	4.8	–
Yang et al. 2021a [87]	China	OBS	124	124 (100)	*EGFR*	2L	OSI	60	–	–	–
							AFA	64	–	–	–
Yang et al. 2021b [88]	China	OBS	198	198 (100)	*EGFR*	–	Delayed RT	94	73 (77.7)	11.1	38 (40.4)
							Upfront RT	104	45 (43.3)	19.9	79 (76.0)
Yomo et al. 2018 [89]	Japan	OBS	133	133 (100)	*EGFR*	1L +	SRS ± EGFR TKI (GEF, ERL, AFA, OSI)	133	–	–	–
Yu et al. 2019 [90]	China	OBS	261	261 (100)	*EGFR*	1L +	EGFR TKIs (ICO, GEF, ERL)	261	114 (43.7)	–	–
Yu et al. 2021a [91]	China	OBS	205	205 (100)	*EGFR*	1L to 2L	OSI with upfront cranial RT	48	–	24.1	–
							OSI without upfront cranial RT	157	–	17.7	–

Table 3 continued

Author year	Country/ region	Study design	Total patients, *N*	BrM population, *n* (%)	Mutation	Line of therapy	Treatment	Arm, *n*	Asymptomatic BrM, n (%)	CNS-PFS median, months	Intracranial response, n (%)
Yu et al. 2021b [92]	China	OBS	571	571 (100)	*EGFR*	1L to > 2L	EGFR TKI (GEF, ICO, ERL, AFA, OSI), local brain therapies (surgery, WBRT, SRS)	571	–	–	–
Zeng et al. 2022 [93]	China	OBS	1081	293 (27.1)	*EGFR*	1L	EGFR TKI	293	–	–	–
Zhao et al. 2021 [94]	China	RCT	313	92 (29.4)	*EGFR*	1L	APA + GEF	51	–	–	–
							PBO + GEF	41			
Zhao et al. 2019 [95]	China	OBS	344	344 (100)	*EGFR*	2L +	WBRT (TKI-naïve group)	207	0	7.7	–
							WBRT (TKI-resistant group)	137	0	5.4	–
Zhao et al. 2022 [96]	China	OBS	367	367 (100)	*EGFR*	1L	1G EGFR TKI (GEF or ERL)	265	117 (44.1)	–	133 (50.0)
							OSI	102	57 (55.8)	–	69 (68.3)
Zhou et al. 2019 [97]	Asia	RCT	187	67 (35.8)	*ALK*	1L	ALEC	44	–	–	32 (72.7)
							CRIZ	23	–		5 (21.7)
Zhu et al. 2017 [98]	China	OBS	133	133 (100)	*EGFR*	–	1G EGFR TKI + RT	67	–	16	–
							1G EGFR TKI	66	–	11.5	–

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, *ASA* aspirin, *B/C* before or concurrent, *BEV* bevacizumab, *BICNR* blinded independent central neuroradiology review, *BL* baseline, *BRIG* brigatinib, *BrM* brain metastasis, *CER* ceritinib, *CNS* central nervous system, *CRIZ* crizotinib, *CT* chemotherapy, *DOC* docetaxel, *EGFR* epidermal growth factor receptor, *ERL* erlotinib, *GEF* gefitinib, *ICO* icotinib, *iPFS* intracranial progression-free survival, *LOR* lorlatinib, *NE* not evaluable, *NR* not reached, *OBS* observational study, *OSI* osimertinib, *PBC* platinum-based chemotherapy, *PBO* placebo, *PEM* pemetrexed, *PFS* progression-free survival, *pts* patients, *RCT* randomized controlled trial, *RT* radiotherapy, *SA* single-arm, *SC* supportive care, *SRS* stereotactic radiosurgery, *TKI* tyrosine kinase inhibitor, *USA* United States of America, *WBRT* whole-brain radiation therapy, *Y* yes

(afatinib) for first-line or later-line therapy. The other study was conducted in multiple countries in Asia and included 541 participants with *EGFR* mutations treated with targeted therapy (afatinib) for first-line or later-line therapy. Of the 59 observational studies, 75% (n = 44) were conducted in Asia (China, Japan, South Korea, Taiwan, Thailand, and Turkey), eight in North America (USA and Canada), and seven in Europe (France, Germany, the Netherlands, and multi-country). Twenty-seven studies included fewer than 200 patients, 22 included between 200 and 500 patients, and 10 included more than 500 patients (median 208 patients; range 100 to 1081 patients). In the 34 observational studies that reporting age and sex for the brain metastasis population, median age was 58.5 years (range 54–68), and median percentage of female patients was 60.5% (range 37–73%).

Clinical Characteristics

Across the 80 studies that included patients with AGAs, 64 reported data for *EGFR* mutations (with the majority when reported being exon 19 deletions or exon 21 L858R), 14 reported data for patients with *ALK* alterations, and two reported data for both *EGFR* mutations and *ALK* alterations (Table 3). Still, across all 179 of the publications reviewed in the SLR, only a minority of patients with NSCLC and brain metastases (20–30%) had any actionable mutation. No study reported biomarkers specific to brain metastases.

For patients who had NSCLC and brain metastases, most RCTs included only those patients who were asymptomatic and/or neurologically stable at baseline. Similarly, on the basis of 23 observational studies, a range of 12.3–81.5% patients were reported to have asymptomatic brain metastases at baseline (Table 3). Among the three observational studies that reported symptoms, headache, nausea, and mental changes were the most frequently reported [30, 46, 64]. Patients who were asymptomatic were more likely to have been treated with EGFR TKIs only or EGFR TKIs plus SRS compared with patients who were treated with WBRT alone or in combination with another type of therapy.

Brain metastases were more often multisite than single site. The majority of brain metastases reported were located at the cerebral hemispheres and cerebellum. Few studies reported the median time interval between the diagnosis of NSCLC and brain metastases; among those studies that did, the average time to diagnosis was between 1 and 2 years (this average does not include patients who had brain metastases at NSCLC diagnosis) [45, 82, 88]. One Japanese retrospective study noted that the rate and frequency of developing brain metastases were rapid and higher in patients with *EGFR* mutations than in patients without *EGFR* mutations [99]. Similarly, in a Canadian cohort study, patients with *EGFR* mutations were reported to be at higher risk of developing brain metastases than patients without *EGFR* mutations [100].

Clinical Management

Overall, the clinical management reported by studies included in this SLR typically followed respective clinical practice guidelines. In brief, of the 80 total studies, 76 evaluated targeted therapy; 15 evaluated chemotherapy; six evaluated immune checkpoint inhibitors (ICIs)/monoclonal antibodies (mAbs), including bevacizumab, sintilimab, and denosumab; and 29 evaluated radiotherapy. Table 3 provides details on therapeutic regimens evaluated in each study.

Nine RCTs reported data for *EGFR* mutations only, eight of which evaluated EGFR TKIs. Six RCTs evaluated first-line targeted therapy, including aumolertinib, furmonertinib, osimertinib, apatinib, icotinib, gefitinib, and erlotinib plus bevacizumab. One RCT evaluated first- and second-line therapies, including icotinib versus WBRT with or without chemotherapy, and one evaluated second-line therapy with osimertinib versus platinum and pemetrexed-based chemotherapy. One RCT evaluated sintilimab plus a bevacizumab biosimilar plus chemotherapy versus chemotherapy only in

patients who had unsuccessful treatment with an EGFR TKI.

The remaining 10 RCTs evaluated patients with *ALK* alterations. Eight RCTs evaluated first-line targeted therapies (alectinib, brigatinib, ensartinib, lorlatinib, crizotinib, and ceritinib). One RCT evaluated second-line and later-line therapy with ceritinib versus chemotherapy, and one RCT evaluated alectinib versus chemotherapy for third-line therapy.

Among the 59 observational studies, 22 reported first-line therapy, nine reported first-line or second-line therapy, two reported second-line or later-line therapy, 14 reported first-line or later-line therapy, and 10 did not report the line of therapy. For first-line therapy, treatments included targeted therapy (EGFR and ALK TKIs), chemotherapy (platinum- and pemetrexed-based), and radiotherapy (WBRT, SRS, and gamma knife radiotherapy). For second-line therapy, treatments included targeted therapy (gefitinib, erlotinib, and osimertinib). For other lines of therapy and studies that did not report line of therapy, treatments included targeted therapy (EGFR and ALK TKIs), chemotherapy (platinum- and pemetrexed-based), radiotherapy (WBRT, SRS, and gamma knife radiotherapy), and surgery.

CNS Clinical Outcomes

Median central nervous system–progression-free survival (CNS-PFS) and intracranial response (ICR) rates were reported in a minority of studies (n = 24). Studies of *EGFR*-mutated NSCLC and brain metastases continued to assess first- and second-generation EGFR TKIs, often in combination with other agents or radiotherapy. In studies of first- and second-generation EGFR TKI monotherapy, where reported, CNS-PFS and ICR rate did not vary greatly across agents within each study [18, 25, 43]. In the first-line setting, treatment with upfront WBRT with or without concomitant TKIs resulted in the more favorable clinical outcomes compared with treatment with TKIs only or upfront TKIs followed by WBRT. Three observational studies found that median CNS-PFS was longer in patients who had received earlier or upfront versus no or delayed radiotherapy [32, 68, 88]. Additional observational studies found that EGFR TKIs in combination or sequenced with radiotherapy (WBRT and/or SRS) had longer median CNS-PFS than with EGFR TKI monotherapy [24, 27, 30, 34, 38, 82, 98]. Several of these combination studies were utilizing first- or second-generation EGFR TKIs. One study by Yu et al., which compared osimertinib with and without upfront radiotherapy, also resulted in the combination having a longer median CNS-PFS [91].

In one RCT, second-generation icotinib resulted in a CNS-PFS of 10 months compared with 4.8 months with WBRT plus chemotherapy [86]. In one RCT, CNS-PFS with first-line use of third-generation furmonertinib was 20.8 months versus 9.8 months with first-generation TKIs [73]. In another RCT, second-line osimertinib resulted in a CNS-PFS of 11.7 months versus 5.6 months with chemotherapy [63]. In a first-line RCT, the ICR rate with osimertinib was 66% compared with 43% with first-generation TKIs [77]. Similarly, in a first-line observational study, the ICR rate with osimertinib was 68% compared with 50% with first-generation TKIs [96]. In a second-line RCT, the ICR rate with osimertinib was 40% versus 17% with chemotherapy [63].

Eight RCTs evaluated treatment for patients with NSCLC, brain metastases, and *ALK* alterations. Crizotinib continues to be the comparator for the second- and third-generation ALK TKIs. Where reported, these second- and third-generation ALK TKIs consistently demonstrated higher CNS-PFS and ICR than did crizotinib or chemotherapy. CNS-PFS with brigatinib was 24 months compared with 5.6 months with crizotinib [22], and 9.6 months with alectrinib compared with 1.4 months with chemotherapy [81]. ICR rates reached 73% (range 46–73%) with second- and third-generation ALK TKIs versus up to 22% with crizotinib and 21% with chemotherapy [71, 75, 97].

DISCUSSION

Trends in Clinical Management

In terms of clinical management for patients with NSCLC, brain metastases, and AGAs, TKIs were described as potentially exhibiting higher penetration rates through the BBB as they are small molecules and have a good lipid–water partition coefficient. For patients with *EGFR*-mutated NSCLC, EGFR TKIs are the established first-line standard of care. In the treatment of brain metastases, while some countries may continue to rely on first- or even second-generation EGFR TKIs for first-line therapy, evidence has demonstrated that afatinib and osimertinib, as well as other third-generation EGFR TKIs, have better CNS penetration and superior CNS efficacy compared with first-generation options. Similarly, second- and third-generation ALK TKIs are also showing significantly improved CNS efficacy over the previous standard of care, crizotinib. The CNS-PFS and ICR results from both RCTs and observational studies related to these TKIs are continually assessed and reflected in updates across practice guidelines and recommendations globally.

Radiotherapy was found to positively affect the BBB by increasing permeability and the concentration of TKIs in cerebrospinal fluid. Adjuvant radiotherapy, when administered with TKIs, facilitated the TKIs' capacity to cross the BBB, and thus demonstrated favorable anticancer effect. Additionally, patients who were asymptomatic were more likely to have been treated with EGFR TKIs only or EGFR TKIs plus SRS compared with patients who were treated with WBRT alone or in combination with another type of therapy.

Continuing Need for Optimal Management of NSCLC and Brain Metastases

Optimal management of brain metastases in NSCLC remains a high priority with continuing unmet needs. There were limited actionable targets evaluated among the included studies (79 of 80 studies evaluated *EGFR* or *ALK*, and one study evaluated *EGFR*, *ALK*, *RET*, *MET*, or *ROS1*). Still, results favored targeted therapy, as well as a combination of localized therapy and targeted therapy, over chemotherapy. Although there is evidence of the effectiveness of systemic therapies and targeted therapies for treatment of brain metastases, many studies of potentially effective anticancer therapies continue to exclude patients with active brain metastases [101].

Though some benefit was observed, the WBRT studies reviewed in this SLR are likely reflective of outdated practice patterns. In the current treatment landscape, conventional WBRT is generally avoided because it causes more neurocognitive problems than SRS [102, 103]. WBRT is frequently reported as an independent prognostic factor of overall survival along with extracranial metastases and performance score. Overall, WBRT is associated with serious harm, does not prolong survival, and yields poorer quality of life; thus, SRS or SRT has been suggested for treating patients with brain metastases when feasible. Lower incidence of radiotherapy-induced brain damage with SRS versus WBRT can be attributed to SRS's ability to target the high-dose radioactive ray directly at the metastatic brain lesion, resulting in less damage to surrounding normal brain tissues and mitigating the radiotherapy-induced adverse reactions [41, 52]. Of note, in developing countries, first-generation EGFR TKIs and WBRT remain the primary treatment in patients with NSCLC and brain metastases, further highlighting the need for a consistent standard of care for this population [52].

In a retrospective study by Rakshit et al., the authors noted that patients with NSCLC with driver mutations had a high incidence of brain metastases at diagnosis; however, no statistically significant differences in survival outcomes were observed between patients with brain metastases and those without brain metastases [104]. These favorable outcomes for patients with brain metastases were surmised to be related to the use of potent active targeted therapies with good CNS penetration for patients with AGAs. For example, osimertinib has exhibited a protective effect against developing brain metastases, demonstrating an

advancement over its first- and second-generation EGFR TKI predecessors [105].

Another study by Julian et al. found that patients with *KRAS* G12C-positive NSCLC had a higher prevalence of brain metastases compared with patients with *KRAS* wild-type tumors. This finding suggests that more research should be performed to evaluate whether KRAS G12C inhibitors can be beneficial for patients with brain metastases [106]. A systematic review concluded that TKI alone resulted in superior results in comparison with TKI plus radiotherapy in patients with NSCLC and brain metastases [107].

Emerging Therapies

Although the BBB remains the primary focus of emerging therapies for patients with NSCLC and brain metastases, it must be acknowledged that primary and metastatic brain tumors can disrupt the structure of the BBB and form a blood–tumor barrier (BTB) [108, 109]. This BTB permeability appears to aid in the successful transport of not only targeted therapies but also some chemotherapies. Thus, emerging therapies for patients with NSCLC and brain metastases with or without AGAs focus on maximizing opportunities to cross the BBB and BTB.

As such, EGFR TKIs were reported to exhibit higher penetration rates than other systemic therapies. Some studies also suggested that radiotherapy, such as WBRT, demonstrated favorable effects in increasing the permeability and concentration of TKIs in cerebrospinal fluid. Current emerging targeted therapies being evaluated in patients with brain metastases include almonertinib, anlotinib, apatinib, dacomitinib, icotinib, lazertinib, lenvatinib, neratinib, osimertinib, zorifertinib, D-0316 (InventisBio), and TY-9591. Emerging therapies for other actionable alterations include alectinib, crizotinib, ensartinib, and lorlatinib for patients with ALK alterations; crizotinib and entrectinib for patients with *ROS1* mutations; sotorasib and adagrasib for patients with *KRAS* mutations; tepotinib and capmatinib for patients with *MET* exon 14 mutations; pralsetinib and selpercatinib for patients with RET fusions; and dabrafenib plus vemurafenib and dabrafenib plus trametinib for patients with *BRAF*-V600E mutations.

While targeted therapies continue to emerge for those with de novo alterations, as patients move into later lines, therapies no longer work for these AGAs. Thus, it is also important to consider how to treat patients with NSCLC and brain metastases who no longer harbor AGAs. For patients with NSCLC, brain metastases, and no AGAs, immunotherapy has emerged as a new first-line standard of care mostly in combination with or following platinum-based chemotherapy. Emerging therapies for patients without AGAs include immunotherapies targeting programmed death cell (ligand) 1 (PD-1/PD-L1), which are thought to be able to penetrate the BBB, including atezolizumab, camrelizumab, cemiplimab, nivolumab, pembrolizumab, sintilimab, tislelizumab, and zimberelimab. Other emerging treatments noted for patients without AGAs include datopotamab deruxtecan (Dato-DXd; a tropho blast cell-surface antigen 2 [TROP2]-directed antibody–drug conjugate [ADC]), bevacizumab, Endostar (an endostatin), ipilimumab (a CTLA-4 inhibitor), temozolomide, 4-demethyl-4-cholesteryloxycarbonyl-penclomedine, OSE-2101 (a neoepitope vaccine restricted to HLA-A2-positive patients), and patritumab deruxtecan (HER3-DXd; a HER3-targeted ADC).

ADCs are emerging as an effective AGA-agnostic therapeutic option across tumor types and treatment lines. By synergistically combining the specificity of mAbs with the antitumor activity of cytotoxic agents, ADCs selectively bind to cancer cells and deliver their cytotoxic payload directly into cancer cells. Along with US Food and Drug Administration (FDA)-approved T-DXd, which targets HER2 in breast cancer and NSCLC, telisotuzumab-vedotin, Dato-DXd, and HER3-DXd are among several ADCs being investigated in NSCLC. Eight patients with brain metastases experienced a best overall intracranial response of partial or complete response. These findings demonstrate the potential of ADCs to effectively treat patients with brain metastases in later lines of therapy. Further recent data suggest that HER3 may be more abundantly expressed in brain metastases in patients with NSCLC than in

extracranial metastases [110]. On the basis of these data and positive results of ADCs in extracranial disease, brain metastases-specific trials with HER3-targeting agents are warranted.

Generalizability

Most studies included in this review were observational studies, which effectively represent the NSCLC population in a real-world setting and reflect the generalizability of the study population. Additionally, studies in all mutation status subgroups were eligible for inclusion in this review, and results were summarized by patient subgroups, type of therapy, and line of therapy. There were no restrictions on interventions or geography. The outcomes included in this review covered a wide range of topics; as such, the findings could provide a comprehensive understanding of the current landscape of clinical characteristics, clinical management, and emerging therapies for patients with NSCLC and brain metastases with and without AGAs.

Strengths and Limitations

The strengths of this review include following the PRISMA and Cochrane guidelines, using independent reviewers with a process for resolving discrepancies, and utilizing artificial intelligence technology to screen excluded records. The inclusion criteria related to interventions and comparators were left broad to increase generalizability. Furthermore, amendments were made to the protocol in order to focus on the most relevant and robust information available. Most studies focused on *EGFR* mutations or *ALK* alterations, and few on other actionable driver alterations; however, these are the most common AGAs in this patient population. Although the search period started only in 2017, the purpose was to summarize and interpret the most recent findings on this topic on the basis of the latest treatment landscape. While the trials and trial designs differed between studies, all trials included followed the PICOTS eligibility criteria. Overall, this review provides a comprehensive overview of the clinical characteristics, clinical management, and emerging therapies for patients with NSCLC and brain metastases.

Of note, in the studies included in this SLR, a majority of patients were treated with first- and second-generation EGFR TKIs in the first-line setting. With osimertinib as the current standard of care in first-line *EGFR*-mutated NSCLC with brain metastases, this may be an important confounder, given its superior CNS activity in comparison to first-generation TKIs. On the basis of the quality assessment, although the majority of all studies were at low risk of bias, it must be acknowledged that eight of the 19 RCTs included in this subset review were categorized as high risk, and all for deviations from the intended interventions (e.g., non-protocol interventions, non-adherence by patient to assigned intervention) (Table S4). Many of the results from all types of studies supported current practice guidelines and continued to highlight the key treatment gaps for patients with NSCLC and brain metastases.

CONCLUSION

Brain metastases are a poor prognostic factor and are common in NSCLC. This review underscores the continued needs of patients with brain metastases in NSCLC, even in those who have AGAs, likely due to the lack of clear understanding regarding effective transport of therapeutic agents across the BBB. The results of this SLR emphasize the need for therapies that can improve clinical outcomes for this patient population. More data are still needed to confirm these findings, given the differences in trial designs of the trials evaluated in this SLR.

Given the recent advancement in targeted therapies, such as fourth-generation EGFR TKIs, new options may continue to improve CNS-related outcomes. Similarly, with an array of ADCs demonstrating their ability to deliver cytotoxic payload to tumors bearing the target antigen, it may be valid to hypothesize that ADCs might have strong activity in the CNS. Furthermore, brain metastases may increase the permeability of the BBB, allowing a more efficient passage of these drugs into the brain. It is

important to evaluate therapies in patients with active, untreated brain metastases as these patients are often excluded from phase 3 trials because of logistical challenges and higher risks for toxicities [111]. Several approaches are being evaluated to overcome the challenges of the BBB [112]. Further clinical validation and transfer of these strategies to ADCs is planned. Aside from NSCLC, tumor regressions and prolongation of survival have been observed with ado-trastuzumab emtansine (T-DM1) in preclinical mouse models of HER2-positive breast cancer and brain metastases. Given the success of these agents in other tumor types, it is hypothesized that they may also prove to be successful in NSCLC.

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