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REVIEW ARTICLE

Medical Treatment Options for Patients with *Epidermal Growth Factor Receptor* Mutation-Positive Non-Small Cell Lung Cancer Suffering from Brain Metastases and/or Leptomeningeal Disease

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Abstract

Brain metastases and/or leptomeningeal disease (LMD) with associated central nervous system (CNS) metastases are known complications of advanced epidermal growth factor receptor (*EGFR*) mutation-positive non-small cell lung cancer (NSCLC). It is important, therefore, to assess the activity of EGFR tyrosine kinase inhibitors (TKIs) versus such CNS complications. This review explores the literature reporting the intracranial activity of EGFR TKIs, and finds that there is evidence for varying efficacy of the approved agents, erlotinib, gefitinib, afatinib, and osimertinib in patients with CNS metastases. Other EGFR TKIs in development, such as AZD3759, may have a future role as therapeutic options in this setting. Emerging evidence indicates that the second- and third-generation EGFR TKIs, afatinib and osimertinib, effectively penetrate the blood-brain barrier, and therefore represent viable treatment options for CNS lesions, and can reduce the risk of CNS progression. These agents should therefore be considered as first-line treatment options in patients with *EGFR* mutation-positive NSCLC who have brain metastases and/or LMD. While there are currently no prospective data comparing the intracranial efficacy of second- and third-generation EGFR TKIs in this setting, CNS activity and protection offered by different EGFR TKIs should be an additional consideration when making decisions about the optimal sequence of treatment with EGFR TKIs in order to maximize survival benefit in individual patients.

Key Points

Few data exist that have specifically assessed the intracranial activity of EGFR TKIs in patients with *EGFR* mutation-positive NSCLC and brain metastases and/or leptomeningeal disease

Although available data indicate that the first-generation EGFR TKIs, gefitinib and erlotinib (with or without concomitant radiation therapy) have moderate activity in this setting, the second- and third- generation TKIs appear to be more effective at penetrating the blood-brain barrier.

Subanalyses of the prospective LUX-Lung 3, 6, and 7 and FLAURA trials indicate that afatinib and osimertinib are active in patients with CNS lesions. Moreover, both agents appear to reduce the risk of CNS metastasis. These agents should be considered as first-line treatments of choice in patients with *EGFR* mutation-positive NSCLC and brain metastases and/or leptomeningeal disease.

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1 Introduction

The brain is a common site of metastatic spread in patients with advanced non-small cell lung cancer (NSCLC), with brain metastases affecting more than 25% of patients during the course of their disease [1]. NSCLC brain metastases can cause neurological symptoms and an associated deterioration in quality of life, while prognosis is poor for these patients, with a median survival after diagnosis ranging between 1 and 5 months [1–7]. The most common approaches to the treatment of brain metastases are radiation therapy (RT), including whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS), and surgical resection. However, recent evidence has shown that WBRT does not improve overall survival (OS) or overall quality of life compared with supportive care [8]. In practice, the specific therapeutic approach adopted tends to depend on the site and number of lesions [9–12]; for example, SRS is only recommended in the event of a small number of isolated lesions of maximum diameter 4 cm [9].

A small proportion (1–10%) of NSCLC patients develop leptomeningeal disease (LMD), also known as leptomeningeal carcinomatosis (LMC) or neoplastic meningitis, which results from the spread of tumor cells to the leptomeninges, subarachnoid space, and cerebrospinal fluid (CSF) [13–15]. As with brain metastases, prognosis for patients with LMD is poor. Suggested treatment options for patients with LMD include RT, surgery, and intrathecal chemotherapy, but the efficacy of these treatments is limited and no consensus has been reached regarding the best therapeutic strategy [16–19]. In general, traditional chemotherapeutic agents used to treat NSCLC do not cross the blood-brain barrier (BBB), so their role in the treatment of central nervous system (CNS) metastases is limited [20, 21]. However, in some cases, tumor neoangiogenesis and damage of the BBB due to tumor growth may allow chemotherapy drugs to penetrate the CNS, supporting their use in certain patients [22, 23].

A higher incidence of brain metastases has been reported in patients with NSCLC harboring epidermal growth factor receptor (*EGFR*) mutations compared with *EGFR* wild-type (WT) tumors, both at the time of diagnosis and during the course of the disease [24–30]. Interestingly, in general, median OS after diagnosis of brain metastases is significantly longer in patients with *EGFR* mutation-positive versus *EGFR* WT tumors [24–30]. Consequently, EGFR-targeted agents, in particular EGFR tyrosine kinase inhibitors (TKIs)—which are an established systemic treatment options for patients with *EGFR* mutation-positive NSCLC—are of interest in the treatment of brain or CNS metastases in this setting.

This review will explore clinical and preclinical evidence for the activity of EGFR TKIs in the treatment of patients with *EGFR* mutation-positive NSCLC and brain metastases and/or LMD, including their ability to penetrate the BBB, and efficacy outcomes reported in clinical trials, Compassionate Use Program (CUP) settings, and case series/studies.

2 First-Generation EGFR TKIs

2.1 Activity of Erlotinib and Gefitinib in Patients with NSCLC and CNS Metastases

The first-generation, reversible EGFR TKIs erlotinib and gefitinib are able to cross the BBB, although, after administration of standard doses, their concentrations in the CSF are limited compared with those in plasma [31–35]. Both drugs have shown some evidence of intracranial activity in patients with NSCLC. Numerous small trials, retrospective analyses, and case studies assessing the efficacy and safety of gefitinib and erlotinib in patients with brain metastases have been described; these studies are detailed in Table 1 and some of these results are described below.

Several studies indicate that the first-generation EGFR TKIs may be active in patients with *EGFR* mutation-positive NSCLC who present with brain metastases, although there is a paucity of evidence for direct intracranial activity. For example, a prospective phase II study evaluated treatment with either erlotinib or gefitinib in 28 patients with *EGFR* mutation-positive NSCLC and brain metastases [36]. A systemic partial response (PR) was reported in 83% of patients, and stable disease (SD) in 11%. Median progression-free survival (PFS) was 6.6 months and median OS was 15.9 months, with no difference in survival outcomes between erlotinib and gefitinib. However, no information was provided on intracranial activity. A similar study in Korean patients who had never smoked, which also evaluated the efficacy of erlotinib and gefitinib in patients with NSCLC and brain metastases, showed median PFS of 7.1 months and median OS of 18.8 months, with 70% of patients achieving a PR and 13% achieving SD [37]. In a retrospective analysis of 81 patients with *EGFR* mutation-positive NSCLC and brain metastases, Zhang et al. reported similar median PFS in patients treated with gefitinib (9.5 months) or erlotinib (9.0 months) [38]. Another Japanese phase II study assessed gefitinib monotherapy in 41 patients with *EGFR* mutation-positive NSCLC and brain metastases [39]. Surgical resection of brain metastases did not preclude participation; unfortunately, no information was provided on surgical resections. Fifty-six percent of patients had between one and three intracranial lesions, and 44% of patients had four. A response rate of 87.8% was reported, with a median PFS of 14.5 months and a median OS of 21.9 months. As expected, given that it is a known marker of favorable prognosis in patients with *EGFR* mutation-positive NSCLC treated with EGFR TKIs [40, 41], presence of an *EGFR* Del19 mutation was associated with improved survival outcomes compared with the presence of an *EGFR*

Table 1 Summary of studies reporting the efficacy of first-generation EGFR TKIs in patients with NSCLC and CNS metastases

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
Gefitinib	Iuchi et al. [39]		II	Gefitinib (250 mg QD)	$N = 41$; *EGFR* mutation-positive, TKI-naïve patients with brain metastases; surgical resection of the brain did not preclude participation	• ORR: 87.8% • Median PFS: 14.5 months; Del19 was associated with improved PFS vs. L858R (17.5 vs. 10.2 months, respectively; $P = 0.003$) • Median OS: 21.9 months; Del19 was associated with improved survival vs. L858R (30.3 vs. 19.8, respectively; $P = 0.025$)
	Ceresoli et al. [50]	Prospective trial		Gefitinib (250 mg QD) with or without prior WBRT	$N = 41$ (18 with prior WBRT, 37 with prior chemotherapy); patients with NSCLC and brain metastases	• ORR: PR, 10%; SD, 17% • DCR: 27%; higher DCR in patients with prior WBRT • Median PFS: 3 months
Erlotinib	Deng et al. [32]			Erlotinib (150 mg QD), following first- or second-line chemotherapy	$N = 6$ ($n = 4$ with *EGFR* mutations); patients with NSCLC and brain metastases	• ORR: WT *EGFR*, 33.3%; mutant *EGFR*, 50% • Brain metastases response: PR, 33.3%; SD, 33.3% • Median PFS: overall, 2.8 months; mutant *EGFR*, 5.6 months
	Porta et al. [103]	Retrospective analysis of patients from the Spanish Lung Adenocarcinoma Data Base (SLADB) study		First- and second-line erlotinib (150 mg QD)	$N = 69$ ($n = 17$ with *EGFR* mutations); patients with NSCLC and brain metastases	• OR: 14 patients, all of whom had *EGFR* mutations (14/17; 82.4%) • In patients with *EGFR* mutations: PR, 35.3%; CR, 47.1%; SD, 17.6% • In patients with *EGFR* mutations, median PFS: 11.7 months
	Ohara et al. [104]	Case report		Fourth-line erlotinib (150 mg QD), following progression after gefitinib, chemotherapy, and RT	Female, Japanese patient with T790M-positive NSCLC and brain metastasis	• Neurological symptoms (disorientation) resolved • Brain metastases disappeared, but extracranial (lung) primary lesion progressed, resulting in treatment discontinuation
	Ruppert et al. [105]	Case report		Third-line erlotinib (150 mg QD), following gefitinib and chemotherapy	Male with del19 mutant NSCLC with brain metastasis; secondary T790M mutation was identified after stopping EGFR TKI, consistent with development of resistance	• Prolonged disease control (4 months), until liver metastases were detected
	Katayama et al. [106]	Retrospective analysis		Erlotinib (150 mg QD), following prior gefitinib therapy	$N = 7$; 6 patients with *EGFR* mutation-positive NSCLC (1 patient *EGFR* mutational status not available) with brain metastases or LMD; 6 patients had prior WBRT or radiosurgery	• ORR: PR, 3 patients; SD, 3 patients • ECOG PS score improved in 3 patients • Neurological symptoms improved in 5 patients
Gefitinib or erlotinib	Park et al. [36]	Prospective study of first-line EGFR TKI	II	First-line gefitinib (250 mg QD) or erlotinib (150 mg QD)	28; patients with common *EGFR* mutations and metastatic brain tumors	• ORR: PR, 83%; SD, 11% • Median PFS: 6.6 months

Table 1 (continued)

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
	Kim et al. [37]		II	First-line gefitinib (250 mg QD) or erlotinib (150 mg QD)	$N = 23$; Korean, never-smoking patients with brain metastases	• Median OS: 15.9 months; no differences in survival between gefitinib and erlotinib • ORR: PR, 70%; SD, 13% • Median PFS: 7.1 months • Median OS: 18.8 months
	Zhang et al. [38]	Retrospective analysis		First-line gefitinib (250 mg QD) or erlotinib (150 mg QD)	$N = 81$; patients with *EGFR* mutant NSCLC and brain metastases	• Median PFS: gefitinib, 9.5 months; erlotinib, 9.0 months • Median PFS (overall treatments): Del19, 10.4 months; L858R, 8.6 months ($P = 0.408$)
Gefitinib or erlotinib + RT	Zhu et al. [58]	Retrospective analysis		Gefitinib (250 mg QD) or erlotinib (150 mg QD) WBRT (30–40 Gy in 10–20 fractions, 5 days/week) or SRS (15–24 Gy)	$N = 133$ (EGFR TKI alone, $n = 66$; EGFR TKI + WBRT, $n = 63$; EGFR TKI + SRS, $n = 4$); patients with *EGFR* mutations and brain metastases	• Median intracranial PFS: TKI + RT, 16.0 months; TKI, 11.5 months ($P = 0.017$) • Median OS: TKI + RT, 22 months; TKI, 15 months ($P = 0.015$) • Exon 21 mutations: Median PFS and OS were longer with TKI + RT than TKI alone (PFS: 14 vs. 9.5 months, $P = 0.001$; OS: 22 vs. 13.5 months, $P = 0.004$)
	Ma et al. [53]		II	Gefitinib (250 mg QD with WBRT (40 Gy/20f/4w)	$N = 21$; patients with NSCLC and brain metastases	• ORR: 81% • PR, 62%; CR, 19%; SD, 14% • Median PFS: 10.0 months • Median OS: 13.0 months
	Welsh et al. [54]		II	Erlotinib (150 mg QD) + WBRT	$N = 40$; patients with NSCLC and brain metastases	• ORR: 86% • Median PFS: overall, 8.0 months; *EGFR* mutant, 12.3 months; *EGFR* WT, 5.2 months • Median OS: overall, 11.8 months; *EGFR* mutant, 19.1 months; *EGFR* WT, 9.3 months
	Zeng et al. [57]	Retrospective analysis		Gefitinib (250 mg QD) with or without WBRT (40 Gy/20f/4w)	$N = 90$; patients with NSCLC and brain metastases	• ORR: 64.4% vs. 26.7% ($P < 0.001$) for gefitinib + WBRT vs. gefitinib • DCR for brain metastases: 71.1% vs. 42.2% ($P = 0.006$) for gefitinib + WBRT vs. gefitinib • Longer time to progression of brain metastases with gefitinib + WBRT vs. gefitinib (10.6 vs. 6.6 months) • Longer median OS with gefitinib + WBRT vs. gefitinib (23.4 vs. 14.8 months)
	Olmez et al. [56]	Retrospective analysis		Erlotinib (150 mg QD) + WBRT	$N = 7$; patients with NSCLC and brain metastases	• All patients had intracranial disease control

Table 1 (continued)

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
	Lee et al. [51]		II	Erlotinib (100 mg QD) + WBRT (20 Gy/5f), then erlotinib (150 mg QD)	*N* = 80 (erlotinib, *n* = 40; placebo, *n* = 40); patients with NSCLC and brain metastases	• In extracranial sites: PR, 3 patients; SD, 2 patients • Median neurological PFS: 1.6 months for erlotinib or placebo • Median OS: erlotinib, 3.4 months; placebo, 2.9 months
	Lind et al. [52]	Dose-escalation study	I	Erlotinib (100 mg QD or 150 mg QD) + WBRT (30 Gy/10f)	*N* = 11; patients with NSCLC and brain metastases	• Only 1 patient had intracranial progression; 6 patients had extracranial progression • Median PFS: 4.6 months • Median OS: 4.4 months • In 7 patients with follow-up neuroimaging: PR, 5 patients; SD, 2 patients
	Zhuang et al. [55]	Prospective cohort study	II	WBRT (30 Gy/10f) with or without second-line erlotinib (150 mg QD) following failure of chemotherapy	*N* = 54 (WBRT, *n* = 31; WBRT + erlotinib, *n* = 23); patients with NSCLC and brain metastases; patients treated with erlotinib had *EGFR* mutations	• ORR: WBRT, 54.8% (PR, 41.9%; CR, 12.9%; SD, 38.7%; WBRT + erlotinib, 95.7% (PR, 60.9%; CR, 34.8%; SD, 4.4%) • Median intracranial PFS: WBRT, 6.8 months; WBRT + erlotinib, 10.6 months • Median overall PFS: WBRT, 5.2 months; WBRT + erlotinib, 6.8 months • Median OS: WBRT, 8.9 months; WBRT + erlotinib, 10.7 months
AZD3759	Ahn et al. [107]	BLOOM	I	Third-line and beyond, AZD3759 (50–500 mg BID)	*N* = 29 (BM, 21; LM, 5; non-measurable/non-BM or LM, 3); patients with *EGFR* mutations	Overall: • Among 20 patients with BM: tumor shrinkage, 8; confirmed PR, 3; unconfirmed PR, 3 • Among 5 LM patients, 1 patient had CSF clearance of tumor cells and improvement of brain MRI imaging and CNS symptoms
	Ahn et al. [64]	BLOOM	I, expansion cohort	AZD3759 (200–300 mg BID) in TKI-naïve patients	*N* = 20 (BM, 16; LM, 4), TKI-naïve patients with *EGFR* mutations and CNS metastases	• Confirmed disease control: 90% • Confirmed OR: 65% • Best response: PR, 65%; SD, 25%
	Cho et al. [63]	BLOOM	I, expansion cohort	AZD3759 (200–300 mg BID) in TKI-naïve patients	*N* = 18, patients with *EGFR* mutations and LMD	• Best response: PR, 4; SD, 9; CR, 1 • 6/18 patients with extracranial tumors had tumor shrinkage but no confirmed response

CNS central nervous system, *DCR* disease control rate, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *NSCLC* non-small cell lung cancer, *ORR* overall response rate, *OR* overall response, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *QD* once daily, *RT* radiation therapy, *SD* stable disease, *SRS* stereotactic radiosurgery, *TKI* tyrosine kinase inhibitor, *WBRT* whole-brain radiation therapy, *WT* wild-type

L858R mutation. In all of the brain metastasis studies, erlotinib and gefitinib were found to be tolerable, with no unexpected adverse events (AEs) reported. Some further retrospective analyses in unselected patients have also been published but are not discussed here, given their limitations. Administration of erlotinib with pulsed dosing has been investigated as a means of increasing CNS penetration. In patients with *EGFR* mutations, studies have shown that such treatment can delay CNS progression but does not improve PFS versus standard-dose erlotinib [42, 43].

2.2 Erlotinib and Gefitinib in Combination with RT

RT is thought to enhance the permeability of the BBB, thereby increasing the concentration of EGFR TKIs in the CSF [44, 45] and reducing the occurrence of the T790M mutation [46, 47]. Consequently, it is possible that EGFR TKI treatment in combination with RT may improve efficacy outcomes in patients with *EGFR* mutation-positive NSCLC and brain metastases. In preclinical studies, the combination of EGFR TKIs with RT has demonstrated a synergistic effect in human tumor cell lines and xenografts [48, 49]. Several clinical studies (Table 1) have shown that RT with concurrent erlotinib or gefitinib is well tolerated, and although there are few comparisons of EGFR TKI and RT combinations with EGFR TKIs or RT alone, the available studies have shown promising efficacy outcomes [50–57].

A recent retrospective analysis has assessed outcomes in patients with NSCLC and brain metastases who were treated with EGFR TKI treatment alone ($n = 66$) versus EGFR TKIs combined with RT ($n = 67$; 63 received WBRT and 4 received SRS) [58]. Median OS and intracranial PFS were significantly longer in the EGFR TKI plus RT group than in the EGFR TKI monotherapy group. Outcomes were also assessed according to *EGFR* mutation type, showing that, in patients with L858R mutations, the EGFR TKI plus RT group had significantly better median OS and intracranial PFS than the EGFR TKI monotherapy group, while there was no significant difference between treatment groups in patients with Del19 mutations. However, this study did not analyze AEs or changes in neurological symptoms or cognitive function with each treatment. Two other studies showed that combining erlotinib or gefitinib with WBRT resulted in enhanced efficacy, as demonstrated by longer median PFS, median OS, and longer duration of response overall [55–57]. Both of these studies also analyzed the safety profile and toxicity of RT combined with erlotinib/gefitinib; while some AEs were more common with combined therapy, they were mostly mild to moderate in severity. While these are interesting observations, the studies are limited by the retrospective nature of the analyses and the small scale of the studies. Further studies are required to provide additional insights into the efficacy of combined RT and first-generation EGFR TKIs in patients with NSCLC and brain metastases.

2.3 BBB-Penetrating First-Generation TKI: AZD3759

The search for drug candidates that are able to effectively penetrate the BBB and achieve effective concentrations in the CSF without unacceptable toxicities has resulted in the development of the selective EGFR inhibitor, AZD3759 [59, 60]. Preclinical and clinical experience with AZD3759 against CNS lesions is summarized below.

Preclinical studies of AZD3759 were performed with erlotinib as a comparator. In murine models of brain metastasis and LM, AZD3759 (15/mg/kg) exhibited excellent CNS penetration, and achieved concentrations above the pEGFR inhibitory concentration (IC_{50}) for longer than 7 h, compared with 6 h or less for erlotinib [61]. AZD3759 was shown to cause tumor regression, and survival rates were significantly higher than those with erlotinib [61].

Currently, AZD3759 is undergoing clinical evaluation in the phase I BLOOM study, which is assessing both AZD3759 and the third-generation EGFR TKI osimertinib treatment in heavily pretreated patients with *EGFR* mutation-positive NSCLC who had progressed on prior EGFR TKI therapy and had a confirmed diagnosis of LMD [62]. Patients had mostly good ECOG PS (57% ECOG 0/1) and 48% had neurological symptoms. AZD3759 has been found to be well tolerated in patients with LMD previously treated with at least one line of EGFR TKI therapy and chemotherapy. One patient (6%) discontinued treatment due to an AE (skin disorder), and some antitumor activity has been observed at an AZD3759 dose of 200–300 mg twice daily [63]. In this study, 5 out of 18 patients (28%) had a confirmed PR or CR in the brain, and 9 (50%) had a SD (Table 1). Only 6 of 18 patients (33%) with extracranial lesions had tumor shrinkage, with no confirmed PR. Two case studies reported similar AZD3759 trough plasma and CSF concentrations 1 week after the start of treatment, indicating full penetration of the BBB [61]. BLOOM is also assessing AZD3759 in patients with treatment-naïve CNS manifestation. Twenty *EGFR* mutation-positive NSCLC patients, with either brain metastases ($n = 16$) or leptomeningeal metastasis ($n = 4$; three pretreated with WBRT) were treated with AZD3759 (200 or 300 mg twice daily). Fifty-five percent experienced grade ≥ 3 AEs (30% skin-related, 20% gastrointestinal), and the treatment discontinuation rate was 10%. Efficacy data were encouraging, with 15 (83%) patients with measurable brain metastases achieving an objective response (1 complete response); 3 (75%) patients with LMD also achieved an objective response, as did 13 (72%) patients with extracranial manifestations (2 complete responses) [64].

3 Second-Generation TKIs

The ErbB family blocker, afatinib, is the most extensively studied of the second-generation EGFR TKIs; afatinib

irreversibly inhibits signaling from homo- and heterodimers of all ErbB family members (EGFR, human epidermal growth factor receptor 2 [HER2, ErbB2], ErbB3 [HER3], and ErbB4 [HER4]). Other second-generation TKIs are also in development in NSCLC [59]. Of note, results were recently reported from the phase III ARCHER 1050 study, which compared dacomitinib, an irreversible inhibitor of three ErbB family members (EGFR, HER2, and ErbB4, versus gefitinib in treatment-naïve patients with advanced NSCLC [65]. However, no data are currently available describing the effect of dacomitinib in patients with CNS metastases, as these patients were specifically excluded from the ARCHER 1050 study [65]. Another study of dacomitinib in patients with progressive brain metastases (NCT02047747) was recently terminated early [66]. Accordingly, and due to the lack of data for other second-generation EGFR TKIs, here we will focus on the preclinical and clinical evidence which demonstrates that afatinib can penetrate the BBB and is active in patients with advanced NSCLC and brain metastases and/or LMD.

3.1 Preclinical Evidence for Afatinib Activity in NSCLC Brain Metastases

Preclinical studies have shown that afatinib potently inhibits the kinase activity of EGFR, HER2, and ErbB4, with lower IC_{50} than those of erlotinib or gefitinib [67–70]. This potency at relatively low concentrations suggests that afatinib has the potential to provide effective treatment of CNS metastases despite incomplete penetration of the BBB [71, 72]; in addition, afatinib may also remain effective in the CSF after resistance to erlotinib or gefitinib has developed [4]. In a murine model of *EGFR* mutation-positive NSCLC, afatinib dose-dependently inhibited the growth of brain lesions and reduced phosphorylated EGFR (pEGFR) levels, indicating target engagement in the CNS. Moreover, there was a strong positive correlation between plasma and CSF concentrations of afatinib, demonstrating that it can effectively penetrate the BBB at sufficient concentrations to inhibit tumor growth in mice. These findings supported the evaluation of afatinib in patients with NSCLC and brain metastases [73].

3.2 Clinical Evidence for First-Line Afatinib in Patients with Advanced NSCLC with Brain Metastases and/or LMD

The approval of afatinib for the first-line treatment of *EGFR* mutation-positive NSCLC was based on two phase III trials comparing afatinib with platinum-based chemotherapy in this setting; LUX-Lung 3 (conducted globally), and LUX-Lung 6 (conducted in China, the Republic of Korea, and Thailand) [74–76]. More recently, the phase IIb LUX-Lung 7 study compared afatinib with gefitinib in the first-line treatment of *EGFR* mutation-positive NSCLC [77]. All three of these trials permitted enrollment of patients with clinically asymptomatic and controlled brain metastases, and included prespecified subgroup analyses in patients with brain metastases at enrollment [71, 77]. Baseline brain metastases were present in 12% of patients in LUX-Lung 3, 13% in LUX-Lung 6, and 16% in LUX-Lung 7.

In a combined analysis of LUX-Lung 3 and 6 (Table 2), PFS was significantly improved with afatinib versus chemotherapy in patients with brain metastases and common (Del19/L858R) *EGFR* mutations (median 8.2 vs. 5.4 months; hazard ratio [HR] 0.50 [95% confidence interval [CI] 0.27–0.95]; $P = 0.0297$) [78]. In both trials, assessed independently, there was a trend toward improved PFS with afatinib versus chemotherapy in patients with brain metastases and common *EGFR* mutations, and the magnitude of PFS improvement with afatinib was similar to that observed in patients without brain metastases. Furthermore, in LUX-Lung 7 (Table 2), the magnitude of PFS improvement versus gefitinib was similar in patients without, and with, brain metastases (HR 0.74 and 0.76, respectively). PFS difference for afatinib versus gefitinib was not significant for patients with brain metastases given the small sample size ($n = 51$) [77].

In both LUX-Lung 3 and 6, overall response rate (ORR) was significantly improved with afatinib versus chemotherapy in patients with brain metastases and common *EGFR* mutations (LUX-Lung 3 70% vs. 20%, $P = 0.0058$; LUX-Lung 6 75% vs. 28%, $P = 0.0027$), and these response rates were similar to those in patients without baseline brain metastases [71]. No statistically significant OS benefit was observed in patients with brain metastases treated with afatinib versus chemotherapy either in the individual LUX-Lung 3 or 6 trials, or in a combined analysis. It should be noted, however, that afatinib was associated with quality of life benefits versus chemotherapy in both trials [74, 75]. Evidence of the activity of afatinib against brain metastases is further confirmed by a recent competing risk analyses of the LUX-Lung 3 and 6 studies. In patients with a target brain lesion at the start of afatinib treatment, the risk of CNS progression (34%) was lower than the risk of non-CNS progression (48%). De novo CNS progression was observed in only 5% of patients after 24 months. In patients without brain metastases at baseline, the non-CNS progression rate after 24 months was 71% [79]. These data demonstrate that afatinib may delay the development of metastatic disease in the brain. In addition, the brain was not the site of first disease progression in the majority of patients with baseline brain metastases who experienced progressive disease (PD) on afatinib, indicating control of existing brain metastases by afatinib. In both LUX-Lung 3 and 6, the safety profile of afatinib in patients with brain metastases was similar to that in those without brain metastases, with no unexpected AEs reported in both treatment groups [71].

CSF concentrations of afatinib were not assessed in LUX-Lung 3 or 6, but a recent prospective multicenter study

Table 2 Summary of studies reporting the efficacy of second-generation EGFR TKIs in patients with NSCLC and CNS metastases

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
Afatinib	Schuler et al. [71]	LUX-Lung 3	III	First-line afatinib (40 mg QD) vs. cisplatin/pemetrexed (75 mg/m^2 and 500 mg/m^2 once every 21 days, up to a maximum of 6 cycles)	*N* = 345 (*n* = 42 with brain metastases [afatinib, *n* = 27; cisplatin/pemetrexed, *n* = 15], of which *n* = 35 also harbor common *EGFR* mutations [afatinib, *n* = 20; cisplatin/pemetrexed, *n* = 15]); patients with *EGFR* mutation-positive NSCLC and brain metastases	In patients with common *EGFR* mutations: • Median PFS: afatinib, 11.1 months; cisplatin/pemetrexed, 5.4 months • Median OS: afatinib, 19.8 months; cisplatin/pemetrexed, 33.2 months • Rate of CNS progression: afatinib, 45.0%; cisplatin/pemetrexed, 33.3% • Time to CNS progression: afatinib, 15.2 months; cisplatin/pemetrexed, 5.7 months • ORR: afatinib, 70.0%; cisplatin/pemetrexed, 20.0% (*P* = 0.0058) • DCR: afatinib, 95.0%; cisplatin/pemetrexed, 80.0%
	Schuler et al. [71]	LUX-Lung 6	III	First-line afatinib (40 mg QD) vs. cisplatin (75 mg/m^2 every 21 days, up to 6 cycles) and gemcitabine (1000 mg/m^2 on day 1 and day 8)	*N* = 364 (*n* = 49 with brain metastases [afatinib, *n* = 30; cisplatin/gemcitabine, *n* = 19], of which *n* = 46 harbor common *EGFR* mutations [afatinib, *n* = 28; cisplatin/gemcitabine, *n* = 18]); patients with *EGFR* mutation-positive NSCLC and brain metastases	In patients with common *EGFR* mutations: • Median PFS: afatinib, 8.2 months; cisplatin/gemcitabine, 4.7 months • Median OS: afatinib, 22.4 months; cisplatin/gemcitabine, 24.7 months • Rate of CNS progression: afatinib, 21.4%; cisplatin/gemcitabine, 27.8% • Time to CNS progression: afatinib, 15.2 months; cisplatin/gemcitabine, 7.3 months • ORR: afatinib, 75.0%; cisplatin/gemcitabine, 27.8% (*P* = 0.0027) • DCR: afatinib, 89.3%; cisplatin/gemcitabine, 72.2%
	Schuler et al. [71]	Combined analysis of LUX-Lung 3 and LUX-Lung 6	III	LUX-Lung 3: First-line afatinib (40 mg QD) vs. cisplatin/pemetrexed (75 mg/m^2 and 500 mg/m^2 once every 21 days, up to a maximum of 6 cycles) LUX-Lung 6: First-line afatinib (40 mg QD) vs. cisplatin (75 mg/m^2 every 21 days, up to 6 cycles) and gemcitabine (1000 mg/m^2 on day 1 and day 8)	*N* = 91 (*n* = 81 harbor common *EGFR* mutations); patients with *EGFR* mutation-positive NSCLC and brain metastases	In patients with common *EGFR* mutations: • Median PFS: afatinib, 8.2 months; chemotherapy, 5.4 months (*P* = 0.0297) • Median PFS was higher with afatinib vs. chemotherapy in patients with Del19 mutation (9.5 vs. 4.7 months, respectively; *P* = 0.0012); there were no significant differences between treatments in patients with L858R (afatinib, 6.9 months; chemotherapy, 9.7 months)

Table 2 (continued)

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
						• PFS benefit was higher with afatinib compared to chemotherapy in patients who received prior WBRT (13.8 vs. 4.7 months) than in those who did not (6.9 vs. 5.4 months) • Median OS: afatinib, 22.4 months; chemotherapy, 25.0 months; no significant differences were seen between treatments among patients harboring Del19 or L8585R mutations
	Park et al. [77]	LUX-Lung 7	IIb	First-line afatinib (40 mg QD) vs. gefitinib (250 mg QD)	$N = 319$ ($n = 50$ with brain metastases: afatinib, $n = 26$; gefitinib, $n = 24$); patients with common *EGFR* mutation-positive NSCLC and brain metastases	• Median PFS: afatinib, 7.2 months; gefitinib, 7.4 months • Median TTF: afatinib, 8.4 months; gefitinib, 9.3 months
	Hoffknecht et al. [4]	CUP and case report		Afatinib (50 mg/day); all patients pretreated with chemotherapy and erlotinib/gefitinib Case report: fourth-line afatinib (50 mg/day)	$N = 100$ patients with brain metastases or LMD; 74% had *EGFR* mutations (77% of which were Del19 or L858R) Case report: Female patient; age: 59 years; ECOG PS: 3/4; L858R-positive NSCLC with LMD	• ORR: PR, 42%; SD, 39% • TTF: overall, 3.6 months; *EGFR*-mutation-positive vs. WT, 4.0 vs. 1.3 months • Median OS: 9.8 months Case report: • Neurological symptoms diminished • ECOG PS improved to 1/2
	Tamiya et al. [80]	Multicenter trial		Third-line or later afatinib (40 mg/day)	$N = 11$; patients with *EGFR*-mutations and LMD	• ORR 27.3% • Median PFS 2.0 months • Median OS 3.8 months • Survival outcomes superior in patients with G719X mutation-positive tumors (median PFS 5.6 months; median OS 7.0 months)
	Saijo et al. [89]	Case series		Third-line afatinib (40 mg/day) or afatinib (40 mg/day) following RT	$N = 3$; Japanese female patients with *EGFR* common mutations and LMD	Third-line afatinib, $n = 2$ patients with Del19: • Reduction in LMD-associated symptoms after 2 weeks • Improvement in ECOG PS to 1; disappearance of evidence of LMD/brain metastases Afatinib after RT, $n = 1$ patient with L858R: • No improvement in ECOG PS, but levels of consciousness improved • LMD under control after 11 months
	Kuiper et al. [14]	Retrospective cohort analysis		Afatinib with/without cetuximab	$N = 3$; male patients with Del19 mutation and LMD	• Survival following LMD diagnosis was variable: 4.6, 8.7, and 0.2 months in the 3 patients

Table 2 (continued)

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
	Lin et al. [87]	Case report		Afatinib (40 mg/day) plus cetuximab (250 mg/m^2 biweekly)	Female patient with Del19 and LMD	• Regression of brain lesions on MRI and reduction of LMD-associated symptoms after 1 month • PD of the lung after 4 months, but no suggestion of relapse of LMD
	Kawaguchi et al. [86]	Case report		Eight-line afatinib (40 mg/day)	Female patient with L858R and LMD	• Regression of neurological symptoms after 1 week of afatinib treatment • Symptom free after 1 month with ECOG PS improved to 1 • Progression free at 7 months
	Ghosn et al. [85]	Case report		Third-line afatinib (50 mg/day)	Male patient with Del19 and LMD	• Disappearance of meningeal enhancement on brain MRI 10 months after the start of afatinib therapy • Patient alive with no evidence of neurological relapse at 35 months
Afatinib + RT	Baird et al. [81]	Cambridge Brain Mets Trial 1 (CamBMT1); Phase 2 of study is currently ongoing (NCT02768337)	Ib	Afatinib (20 mg QD, escalated to 30 mg and 40 mg) + 2 Gy or 4 Gy targeted RT	*N* = 10; patients with NSCLC (*n* = 6) or breast tumors (*n* = 4) with operable brain metastases	• Phase I (dose defining) of study completed: afatinib 40 mg QD will be used in phase II which compares efficacy • Afatinib dose in resected brain metastases was not correlated with RT dose • No dose-limiting toxicities were identified
	Li et al. [84]	Retrospective analysis		Afatinib (30 or 40 mg/day initial or maintenance dose) + WBRT (mean dose of 2805.9 ± 405.4 cGy)	*N* = *28*; *EGFR* mutation-positive, treatment-naive NSCLC patients receiving afatinib monotherapy (*n* = *11*) or afatinib with WBRT (*n* = *17*)	• ORR: afatinib monotherapy, 81.8%; afatinib + WBRT, 88.2% • Intracranial CR: afatinib monotherapy, 63.6%; afatinib + WBRT, 17.6% ($p = 0.02$) • No significant differences in OS between treatments
Dacomitinib	NCT02047747 [66]		II	Dacomitinib (45 mg/day)	Patients with lung cancer, melanoma, HER2-amplified breast cancer, or HER2-amplified gastric cancer with brain metastases or LMD	Study terminated after 4 patients

CNS central nervous system, *DCR* disease control rate, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *LMD* leptomeningeal disease, *MRI* magnetic resonance imaging, *NSCLC* non-small cell lung cancer, *ORR* overall response rate, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *QD* once daily, *RT* radiation therapy, *SD* stable disease, *TKI* tyrosine kinase inhibitor, *TTF* time to failure, *WBRT* whole-brain radiation therapy, *WT* wild-type

evaluated the rate of penetration of afatinib into the CSF, in patients with *EGFR* mutation-positive NSCLC with LMC [80]. Eleven patients with confirmed LMC, mostly heavily pretreated and with 8 patients having common [Del19/L858R] *EGFR* mutations, were treated with afatinib 40 mg/day; blood and CSF levels of afatinib were assessed on day 8. The level of afatinib in the CSF (median) was 2.9 nM, which is greater than the IC_{50} of afatinib for EGFR [80]. In contrast with the LUX-Lung 3, 6, and 7 studies, which permitted the inclusion of patients with asymptomatic brain metastases only, a case series has also been reported describing five patients from one center who had NSCLC with multiple symptomatic brain metastases [78]. These patients declined WBRT and were treated with afatinib only as first-line treatment. In all five patients, afatinib treatment induced complete remission of brain metastases, which lasted for at least 6 months according to magnetic resonance imaging (MRI) analysis, thus representing a clear clinical benefit.

3.3 Afatinib in Combination with RT

Several studies have assessed the feasibility of combining afatinib with RT. The ongoing CamBMT1 phase Ib study is investigating afatinib penetration into cerebral metastases for patients undergoing neurosurgical resection, directly following low-dose targeted RT. Patients with operable brain metastases from breast or lung origin were treated with afatinib for 11 days prior to surgery on day 12. Patients also received a single fraction of targeted RT on day 10 (2 Gy or 4 Gy). Preliminary results from 10 treated patients showed no dose-limiting toxicities and identified a recommended phase II dose for afatinib of 40 mg/day for monotherapy in both the 2-Gy and 4-Gy arms. Importantly, afatinib concentrations in resected brain metastases were, on average, more than 15-fold higher than those in plasma, independent of the applied dose of radiation [81]. Two recent case reports also indicate that combination of 40 mg afatinib with WBRT (30–35 Gy) is feasible, with no signs of acute or late toxicities [82, 83]. A recent retrospective analysis of 28 treatment-naïve NSCLC patients with brain metastases compared the efficacy of afatinib monotherapy with that of afatinib plus WBRT (afatinib, $n = 11$; afatinib + WBRT, $n = 17$). The ORR was 81.8% and 88.2%, respectively. However, the afatinib monotherapy group had a significantly higher complete response rate for intracranial lesions compared with the combination with WBRT (63.6% vs. 17.6%, respectively; $P = 0.02$), and there were no significant differences between the two treatment groups in OS or time to treatment failure with median time to treatment failure of 14.5 months for afatinib plus WBRT and 18.5 months for patients treated with afatinib monotherapy. These data support the therapeutic benefit of afatinib in treatment-naïve, *EGFR* mutation-positive NSCLC patients with brain metastases, regardless of concomitant radiotherapy [84].

3.4 Clinical Evidence for Afatinib in EGFR TKI-Pretreated Patients with Advanced NSCLC

In an afatinib CUP, patients, some of whom had *EGFR* mutations, were treated with afatinib following progression after at least one line of chemotherapy and one line of EGFR TKI therapy [4]. Among 31 evaluable patients with CNS metastases (brain metastases or LMD), the overall rate of cerebral response to afatinib was 35%, and the median duration of response was 120 days (range, 21–395). The CNS disease control rate (DCR) was 66%.

3.5 Clinical Evidence for Afatinib in Patients with Advanced NSCLC and LMD

Data on afatinib use in patients with LMD are limited, but one prospective trial and several case reports have presented results in pretreated patients (Table 2). In total, data from 21 patients with LMD who received afatinib treatment (including two patients treated with afatinib in combination with cetuximab) have been reported [4, 14, 85–89]. The median age of these 21 patients was 61 years (range, mid 20s–79), 14 were female, and the majority had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 3 or 4 at the start of afatinib treatment. Nineteen patients were pretreated, and 18 had received previous treatment with an EGFR TKI. The most common *EGFR* mutation was Del19 (12 cases), while 6 cases were reported with L858R mutations, and 3 cases with G719X. Across these studies, afatinib treatment resulted in regression of neurological symptoms, often accompanied by a dramatic improvement in ECOG PS. Cerebral remissions were also reported and, in some cases, were long-lasting. The median PFS was approximately 4.6 months, ranging from 0.6 months to 35 months with treatment still ongoing. Of note, most of these studies assessed afatinib levels in the CSF, and showed overall CSF levels ranging from 0.14–2.85 ng/mL, which corresponds to 0.1–9.3 nM. To put this into context, the EC_{50} of afatinib for EGFR is 0.5 nM, and the IC_{50} is 1 nM [68, 69], indicating that afatinib reached sufficient CSF concentrations in these studies to achieve effective inhibition of EGFR in the CNS.

4 Third-Generation EGFR TKIs

Several third-generation EGFR TKIs have been developed. Osimertinib was originally developed to target the gatekeeper *EGFR* T790 M mutation, the predominant mechanism of acquired resistance to first- and second-generation EGFR TKIs (50–70%) of cases [90, 91]. It has demonstrated striking clinical activity in patients with T790M-positive tumors following failure of erlotinib, gefitinib, or afatinib [92, 93]. Osimertinib is also active against activating *EGFR* mutations

(Del19, L858R) but is wild-type sparing and has demonstrated superior PFS versus first-generation EGFR TKIs in a first-line setting, with a favorable tolerability profile [94]. Preclinical and clinical experience with osimertinib against CNS lesions is summarized below.

4.1 Preclinical Evidence for Osimertinib Activity in NSCLC Brain Metastases

Preclinical data indicate that osimertinib penetrates the BBB and has antitumor activity [95]. Studies in cynomolgus monkeys using radiolabeled osimertinib and gefitinib also showed much higher brain exposure to osimertinib versus gefitinib. Investigations in a mouse model of *EGFR* mutation-positive brain metastases showed that osimertinib induced dose-dependent tumor regression [95]. These data suggest the potential for clinical application of osimertinib.

4.2 Clinical Evidence for Osimertinib in Patients with Advanced NSCLC with Brain Metastases

The efficacy of osimertinib in EGFR TKI-pretreated patients with brain metastases was reported in some early clinical cases. In the phase I/II study AURA trial, two case studies were described of patients with *EGFR* mutation-positive NSCLC and baseline brain metastases [95]. PR was achieved in both these cases, indicating the ability of osimertinib to control the growth of intracranial tumors in humans. In the phase I BLOOM study described earlier, osimertinib demonstrated encouraging activity in these patients, with an overall leptomeningeal metastasis (LM) response of 43%, as well as improvement of neurological symptoms. However, it should be noted that the osimertinib dose used in this study (160 mg/day) was double the approved dose. Nevertheless, the increased dose appeared to be well tolerated; only two patients had grade ≥ 3 AEs; one case of grade 3 diarrhea and one case of grade 3 nausea.

Two phase II trials, the AURA extension and AURA2 studies, aimed to evaluate the efficacy and safety of osimertinib (80 mg/day) in patients with T790M mutation-positive NSCLC, with PD following prior EGFR TKI therapy. Pooled data from these two trials were used in a pre-planned subgroup analysis of CNS response [96]. Of 192 patients with baseline brain scans, 50 were evaluable for CNS response. Baseline demographics were generally consistent with the overall populations; 66% had Del19 mutations, 76% had WHO PS 2, and 74% had received prior brain irradiation. The confirmed CNS ORR was 54% (95% CI 39–68%), and 12% of patients had a complete CNS response. Eighty-two percent of patients responded by the time of the first assessment (within 6 weeks), and CNS responses were observed regardless of prior brain radiation. The CNS DCR was 92%, and the median maximum percentage change from baseline in CNS target lesion size was −53% (range, −100% to +80%). The 6- and 12-month PFS rates were 72% and 56%, respectively.

These findings have been substantiated by recent results from the phase III studies, AURA3 and FLAURA (Table 3). In the AURA3 study, the efficacy of osimertinib (80 mg/day) was compared with chemotherapy in patients with T790 M-positive NSCLC with disease progression following first-line EGFR TKI therapy [92]. In patients who were evaluable for CNS response ($n = 46$), CNS ORR was 70% with osimertinib and 31% with chemotherapy (OR, 5.1; 95% CI 1.4–20.6) [97]. Median CNS duration of response was 8.9 and 5.7 months, respectively, and CNS PFS was significantly improved with osimertinib versus chemotherapy (median 11.7 vs. 5.6 months; HR 0.32 [95% CI 0.15–0.69]) [97].

The FLAURA trial examined the benefit of osimertinib in the first-line setting, in patients with NSCLC harboring common *EGFR* mutations, including patients with brain metastases [94]. Improved PFS, response rate, and duration of response were reported with osimertinib compared with the first-generation EGFR TKIs, erlotinib and gefitinib. A subset of 116 patients with brain metastases were included (osimertinib, $n = 53$; erlotinib/gefitinib, $n = 63$), 25% of whom were pre-treated with RT. The improvement in PFS with osimertinib versus erlotinib/gefitinib was the same in patients with brain metastases (HR = 0.47) as those without (HR = 0.46). In the overall population, CNS progression was markedly less frequent with osimertinib (6%) than with erlotinib or gefitinib (15%) [94]. Based on competing risk analysis, the probability of experiencing a CNS progression event (in the absence of non-CNS progression or death) was 5% vs. 18% at 6 months, and 8% vs. 24% at 12 months [98]. The CNS ORR was 66% vs. 43%; duration of response was 15.2 vs. 18.7 months with osimertinib and erlotinib/gefitinib, respectively [98].

5 Conclusions/Key Points

The high rate of CNS progression in patients with *EGFR* mutation-positive NSCLC means that there is a need to identify and characterize treatment strategies which are active against existing brain lesions and also reduce the risk of metastatic spread to the CNS. While EGFR TKIs have been studied extensively in patients with advanced NSCLC, relatively few studies included patients with brain metastases and/or LMD. A number of studies described herein indicate that first-generation EGFR TKIs may have some activity in patients with *EGFR* mutation-positive NSCLC and CNS metastases. However, emerging evidence suggests that second- and third-generation TKIs may be better treatment options. The ability of different TKIs to target existing brain

Table 3 Summary of studies reporting the efficacy of the third-generation EGFR TKI osimertinib in patients with NSCLC and CNS metastases

EGFR TKI	Publication	Study description		Treatments	Patient characteristics	Results
		Name/type	Phase			
Osimertinib	Yang et al. [62]	BLOOM	I	Osimertinib (160 mg/day)	*N* = 32; patients with *EGFR* mutations and LMD (*n* = 11 with T790M mutation)	• 23 patients reached radiological assessment: 10 had improvements, 13 had SD • Same 23 patients reached 12-week neurological assessment: 8 symptomatic patients, 7 improved and 1 had SD; of 15 asymptomatic patients, 2 worsened and 13 remained asymptomatic
	Goss et al. [96]	Pooled analysis of AURA and AURA2	II	Osimertinib (80 mg/day) following prior EGFR TKI therapy	*N* = 50; patients with T790M mutation and brain metastases	• CNS ORR: 54%; CNS CR: 12% • CNS responses observed in 82% of patients within 6 weeks, regardless of prior RT • Median CNS PFS not reached
	Mok et al. [92]	AURA3	III	Osimertinib (80 mg/day) following prior first-line EGFR TKI therapy vs. chemotherapy (IV pemetrexed 500 mg/m^2 plus either carboplatin or cisplatin)	*N* = 419 (osimertinib, *n* = 279; platinum-pemetrexed, *n* = 140); patients with T790M mutation and CNS metastases (osimertinib in patients with CNS metastases, *n* = 93; platinum-pemetrexed, *n* = 51)	• Median PFS: osimertinib, 8.5; chemotherapy, 4.2 months • ORR: osimertinib, 71%; chemotherapy, 31%
	Soria et al. [94]	FLAURA	III	First-line osimertinib (80 mg QD) vs. standard of care (erlotinib [150 mg QD] or gefitinib [250 mg QD])	*N* = 116 (osimertinib, *n* = 53; erlotinib/gefitinib, *n* = 63); patients with Del19 or L858R *EGFR* mutations and brain metastases	• Median PFS, osimertinib, 15.2 months; erlotinib/gefitinib, 9.6 months • CNS progression: osimertinib, 6%; erlotinib/gefitinib, 15% (all patients, *N* = 556)

BID twice daily, *BM* brain metastases, *CNS* central nervous system, *CR* complete response, *CSF* cerebrospinal fluid, *EGFR* epidermal growth factor receptor, *IV* intravenous, *LM* leptomeningeal metastases, *LMD* leptomeningeal disease, *MRI* magnetic resonance imaging, *NSCLC* non-small cell lung cancer, *ORR* overall response rate, *OR* overall response, *PFS* progression-free survival, *PR* partial response, *QD* once daily, *RT* radiation therapy, *SD* stable disease, *TKI* tyrosine kinase inhibitor

metastases and to mitigate the risk of CNS progression are important considerations when contemplating treatment decisions, especially with regard to how best to utilize different EGFR TKIs in sequence. Higher BBB penetrance with afatinib and osimertinib, compared with the first-generation agents erlotinib and gefitinib, may lead to greater CNS efficacy; this is supported by evidence from the LUX-Lung 3, 6, and 7, and FLAURA studies [77, 94]. These studies provide supportive evidence for osimertinib and afatinib as first-line treatments of choice (in preference to first-generation TKIs) in patients with CNS involvement; both drugs have clinical CNS benefit, and appear to delay the onset of metastatic disease in the brain. In the absence of studies directly comparing second- and third-generation EGFR TKIs in this setting, there is no clear first-choice EGFR TKI, and treatment decisions must be based on indirect comparisons of safety and efficacy data from across the published studies; other factors likely to influence treatment decisions may include clinical experience, patient preference, cost, and reimbursement. Another consideration is the likely availability of targeted treatment options for second-line and later lines of therapy. More information is required on the development of acquired resistance mechanisms, both generally and in CNS lesions. Currently, resistance mechanisms to osimertinib are not well defined and appear heterogeneous [99–102]. In contrast, the main mechanism of acquired resistance to afatinib in primary tumors is the emergence of T790M mutations (50–70% of cases). If the emergence of T790M is identified as the predominant mechanism of afatinib resistance for CNS lesions, then most patients with brain metastases could benefit from sequential therapy with afatinib followed by osimertinib. On the other hand, given that some patients will progress on afatinib via T790M-independent mechanisms and that other patients will not survive beyond first-line therapy, reserving osimertinib for second-line use will preclude its use in some patients. Prospective comparison of sequential EGFR-TKI regimens is required to define the optimal treatment strategy in patients with *EGFR* mutation-positive NSCLC, including those with CNS lesions.

In summary, while erlotinib and gefitinib have shown some efficacy in patients with *EGFR* mutation-positive NSCLC and CNS metastases, and other EGFR TKIs such as AZD3759 may prove promising as future therapeutic options in this setting, at present, the strongest data support afatinib and osimertinib treatment in this patient population. Additional large-scale studies conducted specifically in patients with *EGFR* mutation-positive NSCLC and CNS metastases should shed more light on the differences between EGFR TKIs, and may reveal the treatment strategies that yield the greatest benefits and improvements in OS for most patients.

Compliance with Ethical Standards

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