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REVIEW ARTICLE

Brain metastases in non-small-cell lung cancer: are tyrosine kinase inhibitors and checkpoint inhibitors now viable options?

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ABSTRACT

Significant progress has been made in the treatment of stage IV non-small-cell lung cancer (NSCLC); however, the prognosis of patients with brain metastases remains poor. Resection and radiation therapy remain standard options. This issue is an important one because 10% of patients with NSCLC have brain metastases at diagnosis, and 25%–40% develop brain metastases during their disease. Standard chemotherapy does not cross the blood–brain barrier. However, there is new hope that tyrosine kinase inhibitors (TKIs) used in patients with identified targetable mutations such as mutations of *EGFR* and rearrangements of *ALK* could have activity in the central nervous system (CNS). Furthermore, immunotherapy is increasingly becoming a standard option for patients with NSCLC, and interest about the intracranial activity of those agents is growing. This review presents current data about the CNS activity of the available major TKIs and immunotherapy agents.

Key Words Non-small-cell lung cancer, NSCLC, epidermal growth factor receptor, *EGFR*, tyrosine kinase inhibitors, TKIs, afatinib, osimertinib, *ALK*, crizotinib, alectinib, ceritinib, immunotherapy, nivolumab, pembrolizumab

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INTRODUCTION

Significant advances have been made in the management of non-small-cell lung cancer (NSCLC) in recent years, but in reality, most patients are not cured of their disease. At diagnosis, approximately half of all patients have metastatic disease, and even those with earlier-stage disease are likely to experience recurrence[1,2]. Although patients with stage IV NSCLC have generally benefited from the progress made in systemic therapy, the prognosis for patients with brain metastasis is considerably poorer. Median survival for such patients is only 1 month in the absence of treatment, 2 months when given glucocorticoid therapy[3–10], and in the range of 2.4–4.8 months despite treatment of cerebral metastatic disease with whole-brain radiation therapy (WBRT)[6].

The lack of effective treatment options is certainly a major issue considering that 10% of patients with NSCLC have brain metastases at diagnosis[11] and that a further 25%–40% will develop brain metastasis during the course of their disease[12]. Yet despite the high incidence of brain metastasis in NSCLC, patients with such metastases are commonly underrepresented in clinical trials of systemic therapies[3,7,8].

The effectiveness of the standard cytotoxic chemotherapy used in NSCLC, mainly platinum doublets, is limited with respect to the treatment of brain metastases because of poor penetration of the blood–brain barrier. Recent advances in our understanding of genomic alterations in lung cancer have led to the discovery of several driver mutations in NSCLC[13]. The most common are the *EGFR* activating mutations, which are present in 50% of patients of Asian descent and in 10%–15% of white patients with NSCLC of adenocarcinoma histology[14]. The second most common targetable driver mutations are *ALK* gene rearrangements, which occur in 3%–5% of NSCLC patients[13,15,16]. Several small-molecule tyrosine kinase inhibitors (TKIs) have been developed and have shown efficacy in targeting the associated pathways, thereby improving clinical outcomes.

A growing body of evidence supports a certain efficacy of the small-molecule TKIs in the central nervous system (CNS)[17]. Whether that efficacy is sufficient to allow patients with brain metastases and targetable mutations to forego local treatment (radiation therapy or surgery) to the brain is now the subject of much debate. Furthermore, a similar question could be asked about immunotherapy. Indications

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for checkpoint inhibitors in NSCLC are rapidly becoming more numerous, and the question of their intracranial efficacy is just starting to be answered. Even the optimal radiotherapy treatment is controversial. In a recent large multi-institutional retrospective study, stereotactic radiosurgery was observed to confer a survival advantage, compared with WBRT, for patients with 4 brain metastases of less than 4 cm[18]. Additionally, evidence suggests that there might not be an advantage in quality of life when WBRT is compared with dexamethasone alone[19]. In essence, there might not be a single answer to this question because several factors—including the number of metastases (single or multiple), the context of the discovery (at diagnosis or upon progression), and the presence of symptoms—might influence the decision.

In the present review, we offer an update about the use of TKIs in patients with brain metastasis, reflecting the currently available data.

BRAIN METASTASIS AND EGFR TKIs

First-Generation EGFR TKIs

First-generation EGFR TKIs, including gefitinib and erlotinib, lead to the inhibition of EGFR by reversibly binding to the kinase domain of the receptor[20]. Both agents have demonstrated efficacy as first-line options for patients with *EGFR* activating mutation–positive NSCLC[21].

Brain metastases occur in approximately one third of patients with activating *EGFR* mutations during EGFR TKI treatment[22]. A pooled analysis of sixteen retrospective and prospective published trials included 464 patients with brain metastases[23]. Of those patients, 102 had *EGFR* activating mutations. An overall benefit of the agents was demonstrated with a pooled objective intracranial response rate (ICRR) of 51.8%, an intracranial disease control rate of 75.7%, a median progression-free survival (PFS) of 7.4 months, and an overall survival (OS) of 11.9 months (Table I). Pooled results were more favourable in the subgroup of patients harbouring *EGFR* activating mutations. The objective response rate (ORR) was 85.0%; the disease control rate (DCR), 94.6%; the PFS, 12.3 months; and the OS, 16.2 months (Table I)[23].

In the case of erlotinib, standard oral dosing of 150 mg daily has limited penetration into the CNS. However, at a high oral pulsatile intermittent dose of 1500 mg weekly, erlotinib achieves cerebrospinal fluid (CSF) concentrations exceeding the half maximal inhibitory concentration[23]. In *EGFR*-positive patients with brain metastases or leptomeningeal disease, that schedule led to a median time to CNS progression of 2.7 months (range: 0.8–14.5 months) and a median OS of 12 months [range: 2.5 months to not reached (NR); Table I][23].

Second-Generation EGFR TKIs

The second-generation EGFR TKI afatinib irreversibly inhibits the tyrosine kinase activity of EGFR by forming covalent bonds with the receptor[28], leading to EGFR inhibition that is more prolonged and potent than that achieved with first-generation EGFR TKIs[20,28,29].

The large open-label randomized phase 3 trials LUX-Lung 3 and LUX-Lung 6 compared oral afatinib 40 mg daily with standard platinum doublet chemotherapy (cisplatin–pemetrexed in LUX-Lung 3 and cisplatin–gemcitabine in LUX-Lung 6) in patients with stage IIIB/IV NSCLC harbouring *EGFR* activating mutations (Table I). The LUX-Lung 3 trial was global; LUX-Lung 6 included patients from several Asian countries. The primary endpoint of PFS was shown to be statistically superior in favour of afatinib in both trials. Both trials also included patients with clinically asymptomatic and controlled brain metastases. "Controlled brain metastases" was defined as metastases that were stable for at least 4 weeks or that did not require treatment with either anticonvulsants or corticosteroids. Leptomeningeal disease was excluded[30–33].

Of the randomized patients (345 in LUX-Lung 3 and 364 in LUX-Lung 6), 42 and 49 respectively had brain metastases. In this pre-specified subset of patients, median PFS was 11.1 months for those receiving afatinib compared with 5.4 months for those receiving chemotherapy in LUX-Lung 3 [hazard ratio (HR): 0.54; $p = 0.14$] and 8.2 months compared with 4.7 months in LUX-Lung 6 (HR: 0.47; $p = 0.11$)[25]. The differences were not statistically significant, possibly because of small sample sizes. In an exploratory combined analysis of both trials, afatinib was superior to chemotherapy in patients diagnosed with *EGFR* activating mutation–positive NSCLC with brain metastases (median PFS: 8.2 months vs. 5.4 months; HR: 0.50; $p = 0.0297$)[33].

It is interesting to note that the benefit of afatinib compared with chemotherapy appeared to be more pronounced in patients with the del19 *EGFR* mutation. In that group, the PFS favoured afatinib compared with chemotherapy, the median PFS being 9.5 months compared with 4.7 months (HR: 0.24; $p = 0.0012$). No difference in OS was observed in either trial, and in the combined dataset, the median OS was 22.4 months with afatinib and 25.0 months with chemotherapy (HR: 1.14; $p = 0.64$) which was not statistically different[33].

Intracranial complete response was not assessed in either LUX-Lung 3 or LUX-Lung 6; however, findings from a compassionate-use program[4,5,25], which included 100 patients with brain metastases and leptomeningeal disease, comparing them with 100 patients not having CNS disease, showed that 35% of the patients with brain metastases experienced an intracranial response. The median time to treatment failure was similar at 3.6 months in both groups. Those findings seem to indicate that afatinib has activity in the CNS.

Third-Generation EGFR TKIs

The third-generation EGFR TKI osimertinib leads to potent and irreversible inhibition of EGFR and also of T790M, the most common resistance-inducing mutation in patients treated with first-line EGFR TKIs[34]. The efficacy of osimertinib in patients with brain metastases was assessed in a pooled analysis of two single-arm phase 2 studies[27]: the AURA extension trial[35] and the AURA2 trial[36]. The overall pooled population consisted of 411 patients (Table I) who had advanced NSCLC with *EGFR* activating mutations and who had progressed on first-line EGFR TKI and were expressing a T790M mutation. Osimertinib was given to all patients at a daily oral dose of 80 mg.

TABLE I Efficacy of EGFR inhibitors in non-small-cell lung cancer with brain metastases

Reference (study name)	Treatment	Intracranial disease		Survival	
		Control rate (%)	Response rate (%)	Progression-free (months)	Overall (months)
Grommes *et al.,* 2011[23]					
Pooled analysis of published data	Erlotinib or gefitinib	75.7	51.8	7.4	11.9
Pooled analysis in *EGFR*-positive patients	Erlotinib or gefitinib	85.0	94.6	12.3	16.2
Retrospective analysis	Pulsatile high-dose weekly erlotinib	Not described	67	2.7 (CNS)	12
Ahn *et al.,* 2016[24] (BLOOM)	AZD3759	Not described	52.4 (measurable)	Not reported	Not reported
Schuler *et al.,* 2016[25]					
(LUX-Lung 3)	Afatinib	Not assessed	Not assessed	11.1	19.8
	Cisplatin–pemetrexed			5.4	33.2
				(HR: 0.54; p=0.14)	(HR: 1.15; p=0.75)
(LUX-Lung 6)	Afatinib	Not assessed	Not assessed	8.2	22.4
	Cisplatin–gemcitabine			4.7	24.7
				(HR: 0.47; p=0.1060)	(HR: 1.13; p=0.7315)
(LUX-Lung 3 and 6 combined)	Afatinib	Not assessed	Not assessed	8.2	22.4
	Cisplatin-based chemotherapy			5.4	24.7
				(HR: 0.50; p=0.0297)	(HR: 1.14; p=0.6412)
Yang *et al.,* 2016[26] (BLOOM)	Osimertinib	Not described	76 (33 LM improvement; 43 LM stable disease)	Not reported	Not reported
Goss *et al.,* 2017[27]					
Pooled data from AURA II and AURA extension	Osimertinib	92 (95% CI: 81 to 98)	54 (95% CI: 39 to 68)	Not reached (95% CI: 7 to not reached)	Not reported

CNS = central nervous system; HR = hazard ratio; LM = leptomeningeal metastases.

Brain images from the 192 patients who underwent baseline computed tomography or magnetic resonance imaging of the brain were evaluated by blinded independent central review. Of those 192 patients, 128 had CNS lesions. For the pooled phase II analysis, only the 50 patients determined to have measurable disease were included. Before study entry, brain radiotherapy had been administered to 74% of those patients. A decrease in the size of the target brain lesions was seen in most patients (CNS ORR: 54%; 95% CI: 39% to 68%; Table I). The median best percentage change in target lesion size from baseline was 53% (range: 100% decrease to 80% increase). The complete response (CR) rate was 12%, and the time to response was rapid, with 82% of patients responding by the time of the first assessment (within 6 weeks). The CNS DCR was 92% (95% CI: 81% to 98%). Prior brain radiation did not affect response to treatment in the CNS. At a median follow-up of 11.2 months, the median CNS PFS was not reached (95% CI: 7 months to NR). At 6 months, the CNS PFS was 72% (95% CI: 57% to 83%); at 12 months, it was 56% (95% CI: 53% to 70%)[27].

The recent phase III AURA3 trial of osimertinib compared with a platinum–pemetrexed combination in randomized patients with T790M-positive NSCLC that had progressed on first-line EGFR TKI demonstrated superior efficacy for osimertinib in both PFS and ORR[37]. The trial permitted the inclusion of patients who had stable asymptomatic CNS metastases and who had been tapered off glucocorticoids for 4 weeks. The updated results of the trial were recently presented[38]. At baseline, CNS metastases were present in 75 of the 279 patients assigned to osimertinib and in 41 of the 140 patients assigned to chemotherapy. Of the latter patients, 37% in the osimertinib group and 49% in the chemotherapy group had received prior treatment to the CNS. Measurable CNS disease was identified in 30 patients receiving osimertinib and in 16 patients receiving platinum-based chemotherapy. In patients with measurable disease, the intracranial response was significantly greater with osimertinib than with chemotherapy, with a CNS ORR of 70% compared with 31% (odds ratio: 5.13; p = 0.015). Compared with their counterparts without CNS disease, the subgroup of patients with CNS metastases experienced a similar PFS benefit with osimertinib (HR when CNS metastases were present: 0.32; $p < 0.001$; HR in the absence of CNS metastases: 0.40;

$p < 0.001$). The median PFS in patients with CNS metastases was 11.7 months with osimertinib and 5.6 months with the platinum doublet (HR: 0.32; $p = 0.004$)[38].

LEPTOMENINGEAL DISEASE IN PATIENTS WITH *EGFR* ACTIVATING MUTATIONS

Options for NSCLC patients with leptomeningeal metastases remain limited—in part because of the frequent exclusion of such patients from clinical trials. The phase I BLOOM trial assessed the safety, tolerability, pharmacokinetics, and activity of osimertinib and AZD3759 in patients with brain metastases and specifically with leptomeningeal disease in *EGFR*-positive NSCLC (Table I)[26].

Oral osimertinib was given at an increased dose of 160 mg daily to patients who had previously received EGFR TKIs. Preliminary data were reported for a 21-patient cohort who were *EGFR*-positive and who had stable extracranial disease (a second cohort of patients who are T790M-positive is currently accruing). All 21 patients in the original cohort were Asian. A T790M mutation was detected in the CSF of 2 patients and in the plasma of 6 patients. Of the 21 patients in the cohort, 5 showed neurologic improvement. Best intracranial response was determined using follow-up magnetic resonance imaging, confirming responses in 7 patients and stable disease in 9. In another 2 patients, CSF cytology confirmed clearance. At the most recent update, 15 patients remained on treatment, 7 of whom had been on treatment for more than 9 months, supporting a durable clinical benefit.

The toxicity profile at the 160 mg dose was predictable and manageable. Grade 3 or greater toxicities were identified in 9 patients, but were determined to be drug-related in only 3 patients. Dose interruption and reduction were necessary in only 2 patients: for skin pruritus in one, and for neutropenia in the other.

The BLOOM trial also assessed AZD3759, a reversible EGFR TKI with high passive permeability at the blood–brain barrier (Table I)[24,26], in the context of leptomeningeal metastases in EGFR TKI–pretreated or –naïve patients and of brain metastases in EGFR TKI–naïve patients[24]. Prior CNS treatment was permitted, and 34% of patients had already undergone WBRT.

Early results have been encouraging. Of the 21 patients with brain metastases included, 11 demonstrated tumour shrinkage. A partial response (PR) was confirmed in 3 patients, and a further 3 patients experienced an unconfirmed PR[24].

ALK-REARRANGED NSCLC

Intracranial Efficacy of Crizotinib

A pooled retrospective analysis assessing the efficacy of oral crizotinib 250 mg twice daily in patients with *ALK*-rearranged NSCLC and brain metastases[39] included data from patients enrolled in the PROFILE 1005 trial[40] and patients randomly assigned to crizotinib in the PROFILE 1007 trial[41] (Table II). Patients were eligible if they had measurable asymptomatic treated or untreated brain metastases at baseline, which resulted in a total population of 888 patients. Within that total patient population, three groups of patients were defined: patients with previously untreated brain metastases (12%, $n = 109$), patients previously treated with radiotherapy (19%, $n = 166$), and patients with no detectable brain metastases at baseline (69%, $n = 613$). The three groups were found to be similar in most major baseline characteristics, with the exception that patients with no detectable brain metastases were more often white and slightly older than patients in the other two groups.

The analysis demonstrated ICRRs of 18% in previously untreated patients (95% CI: 5% to 40%) and 33% in previously treated patients (95% CI: 13% to 59%). The median intracranial times to response were relatively short at 6.0 weeks (range: 4.9–12.4 weeks) in the untreated group and 6.4 weeks (range: 5.9–17.7 weeks) in the previously treated group. The median intracranial duration of response (DOR) was 26.4 weeks (range: 6.1–59.3 weeks) in the untreated group. In the previously treated group, the median was not reached (range: 6.0–59.9 weeks). Overall PFS was similar whether brain metastases were present or absent before the initiation of crizotinib. When patients with a history of brain metastases did progress on crizotinib, 70% progressed in the CNS. In contrast, 20% of patients without brain lesions who progressed on crizotinib progressed with brain metastases. The brain therefore remains one of the dominant sites of progression when brain metastases are already present[39].

Prospective Data for the Intracranial Efficacy of Crizotinib

The international multicentric randomized open-label phase 3 PROFILE 1014 trial aimed to demonstrate the efficacy of crizotinib in the first-line treatment of *ALK*-rearranged NSCLC (Table II)[45,46], with a primary endpoint of PFS. Patients with brain metastases were permitted to enrol, with the restriction that the metastases be treated and that the patient remain neurologically stable for 2 weeks with corticosteroids completely tapered. Those who were enrolled were randomly assigned to crizotinib 250 mg orally twice daily or to an intravenous platinum–pemetrexed doublet. Chemotherapy was investigator's choice, with cisplatin (75 mg/m^2) and carboplatin (area under the curve: 5 or 6) both being options. Chemotherapy was administered every 3 weeks for a maximum of 6 cycles. The trial design also included stratification according to performance status, ethnicity, and the presence or absence of brain metastases. Treatment beyond progression in patients for whom clinical benefit was maintained and crossover were both permitted in the study[45,46].

Between January 2011 and July 2013, 343 patients were randomized 1:1. The median PFS was 10.9 months with crizotinib (95% CI: 8.3 months to 13.9 months) and 7.0 months with chemotherapy (95% CI: 6.8 months to 8.2 months), for a HR of 0.45 ($p < 0.001$)[45,46]. No difference in OS was observed (HR: 0.82; $p = 0.36$). Brain metastases were present at baseline in 92 patients. Intracranial time to progression by independent radiologic review was 15.7 months in the crizotinib arm and 12.5 months in the platinum-doublet arm (HR: 0.45, $p = 0.063$). Intracranial DCR was 40% better with crizotinib at 12 weeks ($p = 0.0003$) and 31% better at 24 weeks ($p = 0.006$).

Despite evidence of some activity in the CNS with crizotinib, the brain remains the most common site of

TABLE II Efficacy of Alk inhibitors in non-small-cell lung cancer with brain metastases

Reference (study name)	Treatment	Intracranial disease		Survival	
		Control rate (%)	Response rate (%)	Progression-free (months)	Overall (months)
Costa *et al.,* 2015[39], (pooled analysis of PROFILE 1005[40] and PROFILE 1007[41])	Crizotinib	At 12 weeks:			
	Previous RT	56	18	6.0 (95% CI: 4.3 to 9.9)	Data not mature
	No previous RT	65	33	5.9 (95% CI: 4.2 to 6.9)	
Crino *et al.,* 2016[42] (ASCEND-2)	Ceritinib	80	45	5.4 (95% CI: 4.7 to 7.2)	Data not mature
Gadgeel *et al.,* 2016[43] (pooled data from NP28673and NP28761)	Alectinib	90.0 (mBMets) 85.3 (mBMets or nmBMets, or both)	64.0 (mBMets) 42.6 (mBMets or nmBMets, or both) 35.8 (prior RT) 58.5 (no prior RT)	9.2 (95% CI: 7.4 to 15.9) 8.3 (mBMets or nmBMets, or both) (95% CI: 5.9 to 11.2)	Not available
Kim *et al.,* 2016[44] (ASCEND-1)	Ceritinib	65 (pre-treated) 79 (naïve)	34.5	6.9 (95% CI: 5.6 to 8.7) 18.4 (95% CI: 11.1 to not evaluable)	Data not mature
Solomon *et al.,* 2016[45], Solomon *et al.,* 2014[46] (PROFILE 1014)		At 24 weeks:			
	Crizotinib	56	Not described	9.0	Not reported
	Cisplatin– or carboplatin–pemetrexed	25 (p=0.006)	Not described	4.0 (HR: 0.40; p<0.001)	
Peters *et al.,* 2017[47] (ALEX)		12-Month cumulative incidence of CNS progression:			
	Alectinib	9.4 (95% CI: 5.4 to 14.7)	81 (mBMets) (95% CI: 58 to 95) 59 (mBMets or nmBMets, or both) (95% CI: 46 to 71)	HR: 0.40 (95% CI: 0.25 to 0.64) favours alectinib	Not available
	Crizotinib	41.4 (95% CI: 33.2 to 49.4)	50 (mBMets) (95% CI: 28 to 72) 26 (mBMets or nmBMets, or both) (95% CI: 15 to 39)		
Soria *et al.,* 2017[48] (ASCEND-4)		At 24 weeks:			
	Ceritinib	86.4 (95% CI: 65.1 to 97.1)	72.7 (95% CI: 49.8 to 89.3)	13.6	Data not mature
	Platinum–pemetrexed chemotherapy	50.0 (95% CI: 28.2 to 71.8)	27.3 (95%CI: 10.7 to 50.2)	6.7 [HR: 0.58 (95% CI: 0.36 to 0.92)]	

RT = radiotherapy; CI = confidence interval; mBMets = measureable brain metastases; nmBMets = non-measureable brain metastases; HR = hazard ratio; CNS = central nervous system.

disease progression for patients taking that agent, an observation that might reflect suboptimal blood–brain barrier penetration by the drug or a biologic change in the tumour. It is therefore clear that, if a TKI is to have success in the management of ALK-rearranged NSCLC, it must be able to demonstrate adequate efficacy in preventing intracranial progression[49–51].

Intracranial Efficacy of Ceritinib

Ceritinib is a selective oral TKI targeting ALK, which, compared with crizotinib, offers more potent ALK inhibition. Its potency exceeds that of crizotinib by a factor of 20 and that of alectinib by a factor of 12. Its pharmacokinetics in the CNS are not as clear, although there is evidence in animal models that it crosses the blood–brain barrier[52].

The efficacy of ceritinib has been assessed in several international trials. The updated data from the dose-expansion phase of the open-label multicentric phase I ASCEND-1 trial were recently published[44]. The trial included patients with locally advanced or metastatic *ALK*-rearranged NSCLC that had progressed on either chemotherapy or on an ALK inhibitor. Patients with stable and asymptomatic CNS metastases were permitted to participate. The recommended oral dose of 750 mg daily was given continuously.

Between January 2011 and July 2013, 255 patients were recruited into the study. At baseline, 50% of the patients (21% of the ALK inhibitor–naïve patients and 79% of the ALK inhibitor–pretreated patients) had brain metastases. Most (67%) had been treated with radiotherapy to the CNS[44]. The median duration of follow-up was 11.1 months (interquartile range: 6.7–15.2 months). A retrospective analysis used those data to assess the intracranial response to ceritinib (Table II)[44]. At inclusion, 124 patients were reported to have brain metastases. Of those 124 patients, 94 were confirmed by independent neuroradiologists to have brain metastases on prior imaging. Patients who were ALK inhibitor–naïve accounted for 19 of the 94 patients; the other 75 had been treated with an ALK TKI. Among the treatment-naïve patients, 3 achieved a CR (2 with and 1 without prior radiotherapy), 5 achieved a PR (2 with and 3 without prior radiotherapy), and 7 experienced stable disease (4 with and 3 without prior radiotherapy). No intracranial progressive disease was observed. Among the 75 pretreated patients, 4 achieved a CR (half with prior radiotherapy) and 10 achieved a PR (7 with and 3 without prior radiotherapy). Most ($n = 35$) experienced stable disease (25 with and 10 without prior radiotherapy), and 12 experienced progressive disease (11 with and 3 without prior radiotherapy). The remaining patients in both groups had unknown responses. In the patients with reported responses, the median time to intracranial response was 6.1 weeks (interquartile range: 6.1–12.3 weeks) which was in keeping with the whole-body response. In this retrospective analysis, the intracranial DCR was therefore 79% (95% CI: 54% to 94%)[44].

The follow-up to the ASCEND-1 trial, ASCEND-2, was an international single-arm open-label phase II study. It enrolled patients who had locally advanced and metastatic NSCLC, and confirmed *ALK* rearrangement, and who had progressed after at least 2 lines of therapy[42]. Patients with brain metastases could enrol provided that they were asymptomatic or neurologically stable. Patients were required to have progressed on crizotinib and on platinum-based chemotherapy. Ceritinib was given in the same manner as in ASCEND-1, at a continuous oral dose of 750 mg daily.

Between December 2012 and September 2013, 140 patients were recruited to the trial. Most of the patients (71.4%) had brain metastases at baseline. Prior radiation therapy to the brain had been completed in 72% of the patients[42]. Assessing the intracranial activity of ceritinib was a priority of ASCEND-2, and several preplanned subgroup analyses for the patients with brain metastases were conducted. Among the 100 patients with brain metastases at baseline, 20 had measurable lesions. Of those 20 patients, 45% experienced an intracranial ORR (95% CI: 23.1% to 68.5%), and 80% achieved an intracranial DCR (95% CI: 56.3% to 94.3%; Table II).

The efficacy of ceritinib in the first-line setting was recently assessed in a larger phase III trial. The open-label randomized phase III ASCEND-4 study recruited patients from 28 countries[48]. Patients with locally advanced or metastatic *ALK*-rearranged NSCLC and asymptomatic or neurologically stable brain metastases were allowed to enrol. Eligible patients were randomized to the previously studied dose of oral ceritinib 750 mg daily or to a platinum–pemetrexed doublet (cisplatin 75 mg/m^2 or carboplatin area under the curve 5–6, and pemetrexed 500 mg/m^2) every 3 weeks. Patients randomized to chemotherapy who had at least stable disease after 4 cycles of platinum–pemetrexed continued with pemetrexed as maintenance. The study was stratified for performance status, previous neoadjuvant or adjuvant chemotherapy, and brain metastases. Crossover was allowed. The primary objective was PFS by independent review.

Between August 2013 and May 2015, 376 patients with *ALK*-rearranged NSCLC were randomized 1:1 to ceritinib or chemotherapy. After 4 cycles of platinum–pemetrexed, 73% of patients in the chemotherapy arm received maintenance pemetrexed. At baseline, 121 patients were known to have brain metastases, and 55 of them had measurable disease[48]. The results favoured the ceritinib arm, with those patients experiencing a PFS of 16.6 months (95% CI: 12.6 months to 27.2 months) compared with 8.1 months in the chemotherapy arm (95% CI: 5.8 months to 11.1 months), for a HR of 0.55 ($p < 0.00001$)[48]. The PFS benefit appeared to be consistent in the various subgroups. In patients with brain metastases at baseline, PFS was 10.7 months with ceritinib (95% CI: 8.1 months to 16.4 months) and 6.7 months with chemotherapy (95% CI: 4.1 months to 10.6 months), for a HR of 0.70 (95% CI: 0.44 to 1.12; Table II).

At the time of publication, the OS data were not yet mature. The median OS in the ceritinib group was not reached (95% CI: 29.3 months to not estimable). The median OS was reached for the platinum–pemetrexed group at 26.2 months (95% CI: 22.8 months to not estimable)[48].

Intracranial response was assessed in 44 patients with measurable brain metastases. The intracranial ORR in the ceritinib arm was 72.7% (95% CI: 49.8% to 89.3%), which was significantly higher than the 27.3% in the chemotherapy arm (95% CI: 10.7% to 50.2%)[48]. Most responses were PRs, but 2 CRs occurred in each group. The intracranial clinical benefit rate at 24 weeks or more was 86.4% with ceritinib

(95% CI: 65.1% to 97.1%) and 50.0% with chemotherapy (95% CI: 28.2% to 71.8%).

The authors noted that ASCEND-4 had a higher incidence of patients with brain metastases (32%) and a higher proportion of untreated metastases (59%) than were seen in the phase III studies of crizotinib and alectinib (incidences of 27.9% and 13.6% respectively). The difference was likely attributable to the fact that untreated brain metastases were not an exclusion criterion for enrolment[48]. The trial supported the hypothesis that patients with brain metastases can still achieve favourable clinical benefit from a TKI even without radiotherapy to the brain.

The CNS Efficacy of Alectinib

Earlier trials in the *ALK*-rearranged NSCLC population demonstrated clearly that, despite the high activity of crizotinib in first-line treatment, most patients will still progress within the first year of treatment[53,54], for the important reason that this progression is in the CNS[42]. The potent and highly selective ALK inhibitor alectinib was shown to be active in the CNS[56]. The capacity of alectinib to cross the blood–brain barrier was shown in animals, with measurements demonstrating a high brain-to-plasma drug concentration ratio (0.63–0.94)[56–58]. In humans, the ratio was thought to be closer to 0.5[57]. Expectations that alectinib could improve outcomes in patients with *ALK*-positive NSCLC progressing on first-line treatment were high.

The North American open-label single-group phase II NP28761 trial included patients with stages IIIB–IV *ALK*-rearranged NSCLC who had previously progressed on crizotinib[58]. Neurologically stable patients with asymptomatic brain metastases or leptomeningeal disease could participate in the trial whether they had previously received radiotherapy or not. All patients received oral alectinib at a dose of 600 mg twice daily, which was based on a previous phase I dose escalation study[56].

Between June 2012 and August 2014 (including the dose-finding phase), 87 patients were recruited. Brain metastases were present at baseline in 52 patients (60%), 34 of whom had previously received radiation to the brain. Although those patients were not excluded, none with leptomeningeal disease participated in the trial.

The primary endpoint of the study, the ORR, was 52% (95% CI: 39.7% to 64.6%), with all responses being partial. Of 16 patients with measurable CNS disease at baseline, 11 had previously received radiation to the brain. A CNS CR was achieved in 25% of the patients, and a PR was achieved in 50%, for an intracranial ORR of 75% (95% CI: 48% to 93%; Table II). In the CNS, the DCR was 100% (95% CI: 79% to 100%)[58]. If all 52 patients with CNS metastases were to be included, the CNS ORR would be 40.4% (95% CI: 27.0% to 54.9%), with 25% CRS and 15.4% PRS. Stable disease in the CNS was maintained in 48.1% of patients, for a CNS DCR of 88.5% (95% CI: 76.6% to 95.7%). The median CNS DOR was 11.1 months for patients with measurable lesions (95% CI: 5.5 months to not estimable) and 15.5 months for all patients with CNS disease (95% CI: 11.1 months to 21.5 months). The response rate was higher in patients who had not previously received radiation (n = 18), with a CNS ORR of 66.7% (95% CI: 41.0% to 86.7%) and a CR rate of 55.6%. Only 1 patient had progressive disease. For the 34 patients who had previously received radiation, the CNS ORR was 26.5% (95% CI: 12.9% to 44.4%), with 8.8% experiencing a CR, and 11.8% having progressive disease. The results were encouraging, but it must be noted that they were based on a small number of patients.

Another single-arm phase II trial, NP28673, was a global study that shared the inclusion and exclusion criteria of NP28761[56]. Between June 2013 and April 2014, 138 patients were enrolled, 61% having baseline CNS metastases. The results of both trials allowed for a pooled analysis of 136 patients with CNS metastases[43], including 50 patients with measurable CNS disease at baseline.

In the group of patients with measurable disease, the CNS ORR was 64.0% (95% CI: 49.2% to 77.1%), with 22% CRS. The DCR in the CNS was 90% (95% CI: 78.2% to 96.7%), and the median CNS DOR was 10.8 months (95% CI: 7.6 months to 14.1 months). If all 136 patients with CNS metastases had been included, the CNS ORR would be 42.6% (95% CI: 34.2% to 51.4%), with 27% CRS. The DCR in the CNS was 85.3% (95% CI: 78.2% to 90.8%), and the median CNS DOR was 11.1 months (95% CI: 10.3 months to not estimable)[43]. The CNS ORR in the 95 patients who had previously received radiotherapy to the brain was 35.8% (95% CI: 26.2% to 46.3%); it was 58.5% (95% CI: 42.1% to 73.7%) in the 41 patients who did not receive radiation. The data from the pooled analysis also supported the hypothesis that alectinib has significant activity in the CNS.

Comparing the CNS Activity of ALK Inhibitors

Results of the phase III global ALEX trial comparing alectinib with crizotinib in first-line or treatment-naïve patients with *ALK*-positive NSCLC were presented at the 2017 annual meeting of the American Society of Clinical Oncology. This open-label study randomized 303 patients from 98 sites in 29 countries (152 patients to alectinib and 151 patients to crizotinib)[47,59]. Patients with asymptomatic brain metastases were allowed to enrol. Of the 58 patients with asymptomatic brain metastases (38%) in the crizotinib arm, 36 (62%) did not receive any CNS treatment. In contrast, of the 64 patients with asymptomatic brain metastases (42%) in the alectinib arm, 37 (64%) did not receive any CNS treatment.

The primary endpoint of investigator-assessed PFS was achieved in the trial, being a median 11.1 months in the crizotinib arm (95% CI: 9.1 months to 13.1 months) and not reached in the alectinib arm (95% CI: 17.7 to NR). Thus, alectinib was statistically better than crizotinib, being associated with a 53% reduction in the risk of progression or death (HR: 0.47; 95% CI: 0.34 to 0.65; $p < 0.0001$). The independently-reviewed PFS endpoint also showed superiority for alectinib compared with crizotinib (HR: 0.50; 95% CI: 0.36 to 0.70; $p < 0.0001$), reaching a median PFS of 25.7 months with alectinib (95% CI: 19.9 months to not estimable) compared with 10.4 months with crizotinib (95% CI: 7.7 months to 14.6 months)[47].

Subgroup analysis showed that alectinib was favoured whether CNS metastases were present at baseline or not. In patients with CNS metastases at baseline, the median PFS was 7.4 months with crizotinib, but the median was not reached with alectinib (HR: 0.40; 95% CI: 0.25 to 0.64). When no CNS metastases were present at baseline, the median PFS was 14.8 months with crizotinib and not reached

with alectinib (HR: 0.51; 95% CI: 0.33 to 0.80). Time to CNS progression also favoured alectinib over crizotinib with a cause-specific HR of 0.16 for CNS progression (95% CI: 0.10 to 0.28; $p < 0.0001$). The cumulative incidence of CNS progression at 12 months was 41.4% with crizotinib (95% CI: 33.2% to 49.4%) and 9.4% with alectinib (95% CI: 5.4% to 14.7%). The ORR was 76% with crizotinib (95% CI: 68% to 82%) compared with 83% with alectinib (95% CI: 76% to 89%; $p = 0.09$). Complete responses were achieved by 2 patients in the crizotinib arm (1%) compared with 6 patients in the alectinib arm (4%). Overall, 22 patients in the crizotinib group and 21 patients in the alectinib group had measurable CNS lesions at baseline. For those patients, alectinib demonstrated a CNS ORR benefit (81% vs. 50% for crizotinib), a CNS CR benefit (38% vs. 5%), and a median DOR benefit in the CNS (17.3 months vs. 5.5 months). Based on 75 events in the intent-to-treat population, an OS trend favouring alectinib was observed (HR: 0.76; 95% CI: 0.48 to 1.20; $p = 0.24$). In terms of safety, alectinib was more tolerable than crizotinib, being associated with fewer grades 3 and 4 adverse events (41% vs. 50%). In conclusion, the ALEX trial confirmed that, compared with crizotinib, alectinib is associated with superior and prolonged PFS, suggesting that first-line alectinib might be superior to sequential treatment with crizotinib and alectinib[47].

The foregoing results are in keeping with the published results of the J-ALEX trial, which randomized 207 ALK inhibitor–naïve Japanese patients to crizotinib or alectinib[60]. Because of Japanese drug regulations, alectinib was given at an oral dose of 300 mg twice daily. As in the global ALEX trial, J-ALEX's primary endpoint of median PFS was met, with a HR of 0.34 ($p < 0.0001$) in favour of alectinib. The benefit of alectinib was particularly important in patients with brain metastases at diagnosis for whom a HR of 0.08 (95% CI: 0.01 to 0.61) in favour of alectinib was demonstrated when assessed by independent review[60].

Alectinib should become the new standard of care for patients with previously untreated stages IIIB or IV *ALK*-positive NSCLC. Considering trial results, alectinib should be used in the first line for patients with asymptomatic brain metastases, potentially allowing them to avoid CNS-directed therapy until failure of alectinib or the appearance of neurologic symptoms.

Promising ALK Inhibitors with Intracranial Activity

Several ALK inhibitors currently under investigation have shown CNS activity in early data. The ALK inhibitor brigatinib initially showed, in a post-hoc analysis by independent radiologic review of a single-arm phase I/II trial, a 50% ICRR and an intracranial disease control rate of 85%[61]. Furthermore, recently published data from the phase II ALTA trial in patients with crizotinib-refractory *ALK*-rearranged disease demonstrated impressive CNS responses[62]. The trial compared an oral brigatinib dose of 90 mg daily with an oral dose of 180 mg daily after a 7-day lead-in dose of 90 mg. At baseline, 80 patients in the 90 mg arm and 74 patients in the 180 mg arm had brain metastases. Of the latter patients, 26 in the 90 mg arm and 18 in the 180 mg arm had measurable brain metastases. At the 90 mg dose, the ICRR of 46% was similar to the previously reported results in the phase I/II study. However, at the increased dose of 180 mg, the ICRR reached 67%. The median CNS PFS was 15.6 months in the 90 mg arm (95% CI: 9.0 months to 18.3 months) and 18.4 months in the 180 mg arm (95% CI: 12.8 months to NR). The median CNS DOR was not reached in either arm. The safety profile was also acceptable, with significant grade 3 or greater adverse events of increased creatine kinase (1% at 90 mg and 12% at 180 mg), hypertension (4% at 90 mg and 7% at 180 mg), and increased lipase (4% at 90 mg and 3% at 180 mg)[62].

Lorlatinib was developed as a selective brain-penetrant TKI with activity in patients with both *ALK* rearrangement and *ROS1* mutation. Preliminary results of its phase I/II trial, which enrolled both treatment-naïve and -resistant patients, demonstrated an objective ICRR of 44% in patients with brain metastases and an ICRR of 60% in patients with measurable brain metastases[63].

CNS EFFICACY OF IMMUNOTHERAPY

Given recent advances in immunotherapy, important strides have been made in the treatment of metastatic NSCLC when no targetable driver mutation has been identified. For such patients, brain metastases inevitably required local treatment with either resection, stereotactic radiosurgery, or WBRT. Whether the immunotherapy agents in current use can achieve sufficient intracranial activity to provide a reliable option for patients with CNS disease remains under investigation.

Nivolumab

The CNS activity of the human immunoglobulin G4 anti–PD-1 monoclonal antibody nivolumab was assessed in an Italian expanded-access program associated with the CheckMate 017 trial. CheckMate 017 was a randomized phase III trial that compared nivolumab with docetaxel in patients with metastatic squamous NSCLC that had progressed on platinum-based chemotherapy[64]. Nivolumab was given at an intravenous dose of 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The expanded-access program included 37 patients with asymptomatic and controlled brain metastases[65]. For those patients, the ORR was 19%, with 1 CR and 6 PRs. Stable disease was achieved in 11 patients, leading to a DCR of 49%; 19 patients experienced progression. The median OS was 5.8 months in the group of patients with brain metastases (95% CI: 1.8 months to 9.8 months) compared with 7.9 months for the entire study population (95% CI: 6.2 months to 9.8 months; Table III)[65].

Furthermore, a pooled analysis of the prospective trials CheckMate 063[68], CheckMate 017[64], and CheckMate 057[69] evaluated the efficacy of nivolumab in patients with asymptomatic brain metastases who had received prior radiotherapy and whose asymptomatic brain metastases were untreated. Nivolumab was given at an intravenous dose of 3 mg/kg every 2 weeks; the docetaxel dose was 75 mg/m^2 every 3 weeks. The nivolumab group included 46 patients with brain metastases, and the docetaxel group, 42 such patients.

The results, presented in abstract form[67], showed an ORR of 28% for nivolumab compared with 19% with docetaxel. Disease progression occurred in 39% of the

TABLE III Effect of immunotherapy on brain metastases in non-small-cell lung cancer

Reference (study name)	Treatment	Intracranial disease		Median overall survival (months)
		Control rate (%)	Response rate (%)	
Brahmer *et al.,* 2015[64] (CheckMate 017)	Nivolumab	49	19	5.8 with brain metastases (95% CI: 1.8 to 9.8) 7.9 entire population (95% CI: 6.2 to 9.8)
Goldberg *et al.,* 2016[66] (NCT12085070)	Pembrolizumab	Not described	33	Not described
Goldman *et al.,* 2016[67] (CheckMate 012, arm M)	Nivolumab	Not described	16.7	Not described

CI = confidence interval.

patients receiving nivolumab and in 43% of the patients receiving docetaxel. In patients with previously treated brain metastases, the median OS was 8.4 months in the nivolumab arm (95% CI: 4.99 months to 11.6 months) compared with 6.2 months in the docetaxel arm (95% CI: 4.4 months to 9.23 months).

The efficacy of nivolumab in patients with untreated CNS metastases was also evaluated in arm M of CheckMate 012[67]. That trial enrolled patients with stage IV NSCLC and at least 1 CNS metastasis and no prior local therapy. Patients were not excluded based on histology. In this single-arm trial, all patients received nivolumab 3 mg/kg every 2 weeks until disease progression. Results for the 12 patients included in arm M showed a median OS of 8.0 months (95% CI: 1.38 months to 15.5 months) and a median PFS of 1.6 months (95% CI: 0.92 months to 2.50 months). Responses achieved in 2 patients (1 CR, 1 PR) resulted in an ORR of 16.7% (95% CI: 2.1% to 48.4%)[67]. The other 10 patients in arm M experienced progression.

Additional data are required before conclusions can be drawn about the benefit of nivolumab in patients with brain metastases.

Pembrolizumab

Another human anti–PD-1 antibody, pembrolizumab, has demonstrated efficacy in NSCLC. An ongoing phase II trial at the Yale Cancer Center is assessing the activity of pembrolizumab in patients with untreated or unequivocally progressing brain metastases[66]. The trial has two cohorts, a NSCLC cohort and a melanoma cohort. Patients with NSCLC are required to be PD-L1–positive. The trial has a single arm: all patients are receiving intravenous pembrolizumab 10 mg/kg every 2 weeks. Between March 2014 and May 2015, the NSCLC cohort enrolled 18 patients. Histology in most patients was adenocarcinoma (78%), and most patients had previously received systemic therapy (72%). Slightly more than half the patients (56%) had previously received CNS therapy. Early data showed intracranial responses in 33% of NSCLC patients (95% CI: 14% to 59%), with 4 patients achieving a CR, and 2 patients, a PR (Table III). Pembrolizumab was well-tolerated, with no neurologic adverse events exceeding grade 2. Treatment discontinuation occurred in 1 patient because of grade 3 colitis; other grade 3 or greater adverse events included grade 3 pneumonitis and grade 4 hyperkalemia.

This encouraging trial continues to accrue patients, and updated results are expected in the near future[66].

SUMMARY

Physicians must now take several factors into consideration when managing brain metastases in patients with metastatic NSCLC. Although brain metastases that are symptomatic and immediately life-threatening must still be addressed locally with resection or radiotherapy, the management of asymptomatic brain metastases is not as clear[70].

Increasing evidence now suggests that, in patients harbouring *EGFR* activating mutations, EGFR TKIs have at least some activity in the CNS. Such activity is especially true for the second- and third-generation agents.

Asymptomatic brain metastases are particularly common in patients with *ALK*-rearranged NSCLC. The three principal ALK inhibitors have shown efficacy in treating brain metastases. However, most patients with brain metastases included in major trials had previously been treated with radiotherapy.

The data for the use of immunotherapy in treating brain metastases are encouraging, but studies remain at a very early phase.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AW has received speaker fees from AstraZeneca, Novartis, Pfizer, Jenssen, and Astellas. AW has also received fees as an advisory board member for AstraZeneca, Novartis, Pfizer, Celgene, and Astellas. SMB has received speaker fees from Celgene and Novartis.

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