Abstract. Non-small-cell lung cancer (NSCLC) ranks as a leading cause of cancer-related death globally. Brain metastases are a frequent complication of NSCLC, with 25-40% of patients developing brain metastases during the course of the disease, often within the first 2 years after diagnosis of the primary tumor. Improvements in neurological symptoms and performance status have been reported with whole-brain radiation therapy (WBRT) in combination with steroid therapy in NSCLC patients. In addition, a survival benefit has been reported for patients with a single brain metastasis treated with stereotactic radiosurgery, while clinical outcome is improved with surgery followed by WBRT versus WBRT alone. However, due to their poor performance status, many patients with brain metastases are not eligible for surgery or radiosurgery. Furthermore, the role of systemic chemotherapy for the treatment of brain metastases is controversial due to the impenetrable nature of the blood brain barrier (BBB), with reported response rates to chemotherapy ranging from 15-30% (overall survival [OS] 6-8 months). Response rates of brain metastases to EGFR tyrosine kinase inhibitor (TKI) treatment (e.g. gefitinib, erlotinib, afatinib) in patients with NSCLC harboring EGFR mutations reach 60-80%, with a complete response rate as high as 40%. Median OS is 15-20 months, and progression-free survival in the brain reaches 6.6-11.7 months, demonstrating improved clinical outcome. Metastatic involvement of the CNS appears to be a relatively common complication in patients with ALK-positive NSCLC and the CNS represents a dominant site of progression in ALK-positive patients treated with the ALK TKI crizotinib. In addition, CNS progression on crizotinib contributes substantially to the high levels of morbidity and mortality observed among patients with ALK-rearrangements, a finding that is consistent with low CNS penetration of the drug. Second-generation ALK inhibitors (ceritinib, alectinib) are well-tolerated and demonstrate excellent intracranial activity. The various reports of dramatic and prolonged responses in brain metastases patients treated with EGFR and ALK TKIs suggest that these agents may be a valid treatment option for patients with asymptomatic brain metastases from NSCLC, especially for those with EGFR-activating mutations or harboring ALK rearrangement. However, larger phase III studies are required to fully define the activity of these agents and their place in the therapeutic armamentarium of brain metastases.

Non-small-cell lung cancer (NSCLC) continues to be one of the major causes of cancer-related deaths around the world (1). Brain metastases are a frequent complication of NSCLC (1) with 25-40% of patients developing brain metastases during the course of the disease, often within the first 2 years after diagnosis of the primary tumor (2). The cerebral hemispheres are the most common site for the development of the majority of brain metastases (80%), followed by the cerebellum (15%) and the brainstem (5%) (2).

For patients with brain metastases the outlook is very poor, with a median overall survival (OS) of less than 3 months without treatment, and few effective treatment options (3).
Current treatment options for NSCLC patients with brain metastases include whole-brain radiation therapy (WBRT) with or without stereotactic radiosurgery. Surgery followed by WBRT typically achieves a better outcome versus WBRT; improvements in neurologic symptoms and performance status have been reported with WBRT in combination with steroid therapy, while a survival benefit has been reported for patients with single brain metastases treated with stereotactic radiosurgery (4). However, their poor performance status invariably precludes NSCLC patients with brain metastases from undergoing surgery or radiosurgery. Furthermore, the role of systemic chemotherapy for the treatment of brain metastases is controversial due to the impenetrable nature of the blood brain barrier (BBB). As a consequence, few studies have investigated chemotherapy in this setting. However, systemic chemotherapy continues to remain an essential treatment strategy for disseminated NSCLC, with reports of response rates of 15-30%, and an OS of 6-8 months (5, 6).

In recent years, promising response rates together with a favorable safety profile have been reported in NSCLC patients with brain metastases treated with tyrosine kinase inhibitors (TKIs) (7, 8), suggesting that TKI therapy may represent an attractive treatment option for this patient population. This review presents an overview of currently available data on the use of approved TKIs for the treatment of brain metastases in patients with NSCLC.

TKIs and Brain Metastases – Biology

The inability of the majority of chemotherapeutic drugs to cross the BBB renders most brain metastases resistant to systemic chemotherapy (9). An intact BBB, which comprises endothelial cells, astrocytes, pericytes with tight junctions, and several carrier proteins, regulates the migration of molecules to the brain; small lipophilic molecules (molecular weight <400 Da) are transported via diffusion, while carrier proteins regulate the passage of other molecules. It is because of their large size and hydrophilic nature that most chemotherapeutic agents are unable to cross the BBB, exceptions to this being temozolomide, topotecan, melphalan, carmustine, and irinotecan. The presence of multidrug resistance efflux pumps (e.g., P-glycoprotein) at the BBB also further regulates the passage of drug molecules, potentially limiting drug concentrations at the pharmacologic site of action (10, 11).

In contrast to traditional cytotoxic agents, the permeation of TKIs across the BBB has been demonstrated (12). However, despite their low molecular weight, the cerebrospinal fluid (CSF) concentrations of erlotinib and gefitinib reported in the literature following administration at standard doses are generally just a small fraction of the corresponding plasma concentrations, suggesting that TKIs are typically limited in their ability to permeate into the CSF (13, 14).

TKIs and Brain Metastases – Clinical Data

From standard chemotherapy, the field of advanced or metastatic NSCLC treatment has experienced a paradigm shift. A substantial proportion of patients with NSCLC harbor
specific genetic alterations that affect tumor proliferation and survival, making them sensitive to inhibition of the corresponding activated oncogenic pathway by targeted therapies. This apparent increase in susceptibility has resulted in highly promising response rates and median progression-free survival (PFS), together with quality-of-life improvements, following administration of TKI therapy to patients with EGFR mutation-positive NSCLC (18).

**EGFR TKIs**

Response rates of brain metastases to EGFR TKI treatment (gefitinib, erlotinib, and afatinib, Figure 1) in patients with NSCLC harboring EGFR mutations reach 60-80%, with rates of complete response (CR) as high as 40% reported. Median OS is in the range of 15-20 months, and PFS in the brain reaches 6.6-11.7 months, both significantly longer than for EGFR wild-type tumors (Table I).

**Gefitinib.** Gefitinib (Iressa®, AstraZeneca, UK) inhibits the tyrosine kinase activity of the EGFR pathway. Li et al. (24) retrospectively reviewed the clinical records of 14 NSCLC patients who had brain metastases; their EGFR mutation rate was 64.3% (9/14). All of the patients with an EGFR mutation achieved gefitinib plasma radiotherapy with or without surgery and 88.9% (8/9) experienced an objective response. In addition, Iuchi et al. (22) conducted a phase II study to evaluate the efficacy of gefitinib (without radiation therapy) for the treatment of brain metastases in Japanese patients with EGFR-mutant lung adenocarcinoma (n=41). The overall response rate (ORR) was 87.8%, median PFS was 14.5 months (95% confidence interval [CI], 10.2-18.3 months), and median OS was 21.9 months (95% CI, 18.5-30.3 months). Notably, a significantly better outcome in terms of PFS (p=0.003) and OS (p=0.025) was observed among patients with an exon 19 deletion than among those with an L858R mutation.

In a second phase II study in patients (n=28) with EGFR-mutant NSCLC and brain metastases, treatment with gefitinib or erlotinib once daily was associated with a partial response (PR) in 23 patients (83%) and stable disease (SD) in 3 patients (11%). Median PFS and OS were 6.6 months (95% CI, 3.8-9.3 months) and 15.9 months (95% CI, 7.2-24.6 months), respectively, and did not differ significantly according to the EGFR TKI used. Further evidence of the efficacy of TKI therapy in this setting was provided by data from a Korean study conducted in “never-smoker” patients (n=23) with synchronous asymptomatic brain metastases (20). Following once-daily treatment with gefitinib or erlotinib, a response rate of 69.6% was reported, with 16 of 23 patients achieving a PR and 3 patients achieving SD; the remaining 4 patients had progressive disease. Median PFS and OS were 7.1 and 18.8 months, respectively, and intracranial tumor responses were noted in 17 patients (73.9%).

**EGFR TKIs** have been reported to augment the radiation response in several human carcinoma cell lines *in vivo* and *in vitro* (25, 26). In addition, data from other studies have led to the suggestion that radiation therapy may promote opening of the BBB (27-29), with maximal “opening”, and manageable side effects, achieved with a total radiation dose of 20-40 Gy (fraction size 2 Gy) (30, 31). Combination therapy comprising an EGFR TKI and radiotherapy has been evaluated in several clinical studies with promising results. In a phase II study in a Chinese population with brain metastases from NSCLC (n=21), concomitant treatment with WBRT and gefitinib achieved an ORR of 81%, with a median PFS and OS of 10.0 months and 13.0 months, respectively (32). In a second study, prior treatment with WBRT was reported to confer a statistically significant advantage in terms of disease control rate (DCR) among NSCLC patients with measurable brain metastases treated with daily gefitinib (n=18) (DCR: 56% [10/18 patients] vs. 9% [2/23] for radio-naïve patients treated with daily gefitinib; p=0.0006) (33). Further support for these findings was provided by Zeng et al. (34), who conducted a retrospective analysis of 90 patients with brain metastases from NSCLC who received gefitinib with or without concomitant WBRT. Patients in the gefitinib-WBRT group achieved significantly higher ORR (64.4% vs. 26.7%;

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Selection</th>
<th>Brain RR</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>17</td>
<td>EGFR mutated</td>
<td>82%</td>
<td>NS</td>
<td>Porta et al. (7)</td>
</tr>
<tr>
<td>Gefitinib or Erlotinib</td>
<td>28</td>
<td>EGFR mutated</td>
<td>83%</td>
<td>15.9 months</td>
<td>Park et al. (8)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>9</td>
<td>EGFR mutated</td>
<td>89%</td>
<td>NS</td>
<td>Li (19)</td>
</tr>
<tr>
<td>Gefitinib or Erlotinib</td>
<td>23</td>
<td>Asian never-smokers</td>
<td>74%</td>
<td>18.8 months</td>
<td>Kim et al. (20)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>40</td>
<td>unselected</td>
<td>86%</td>
<td>11.8 months</td>
<td>Welsh et al. (21)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>41</td>
<td>EGFR mutated</td>
<td>88%</td>
<td>21.9 months</td>
<td>Iuchi et al. (22)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>32</td>
<td>EGFR mutated, TKI-pretreated</td>
<td>35%</td>
<td>9.8 months</td>
<td>Hoffknecht et al. (23)</td>
</tr>
</tbody>
</table>

NS: Not stated.
in the CSF was 54 ng/mL and thereby exceeded the median. Erlotinib and OSI-420 were 5.1% (±1.9%) and 5.8% (±3.6%), respectively (37). In another analysis, the concentrations of samples (23.7±13.4 ng/mL) were 717.7±459.7 ng/mL, respectively (p=0.344). Patients with del19 or L858R mutations of EGFR achieved a PFS of 10.4 and 8.6 months, respectively (p=0.408). This study demonstrated no significant differences in efficacy between gefitinib and erlotinib as first-line treatment for patients with brain metastases from advanced NSCLC harboring common EGFR mutations. However, since both TKIs have shown comparable efficacy, the tolerability profile should be taken into account, which clearly favors the use of gefitinib.

Erlotinib. Erlotinib (Tarceva®, Roche, Switzerland) inhibits EGFR signaling by binding to the intracellular tyrosine kinase domain. The penetration of erlotinib into the CSF has been questioned; however, possibly due to the fact that metastases of the CNS of a detectable size may not harbor an intact BBB structure and function (36), crossing of the BBB has been described for erlotinib in lung cancer patients. Using 13C marked erlotinib as a tracer with positron-emission/computed tomography to monitor EGFR therapy, Weber et al. (12) reported accumulation of erlotinib in brain metastases in a non-irradiated patient with NSCLC who had responded to treatment. Still, the ability of erlotinib to permeate into the CSF seems limited. In a study in 6 NSCLC patients treated with erlotinib 150 mg once daily for 4 weeks, the concentration of erlotinib in the CSF was determined using high performance liquid chromatography tandem mass spectrometry. All 6 patients had received prior chemotherapy but were WBRT-naïve. The average erlotinib concentration in the CSF was found to be only 4.4% (±standard deviation 3.2%) as compared to blood plasma samples (23.7±13.4 ng/mL versus 717.7±459.7 ng/mL, respectively) (37). In another analysis, the concentrations of erlotinib and its active metabolite OSI-420 in the plasma and the CSF were determined in 4 patients with NSCLC who had CNS metastases (13). The mean CSF penetration rates of erlotinib and OSI-420 were 5.1% (±1.9%) and 5.8% (±3.6%), respectively. In these cases, the mean concentration of erlotinib in the CSF was 54 ng/mL and thereby exceeded the median inhibitory concentration (IC50) of erlotinib in intact tumor cells with wild-type EGFR gene (20 nmol/l; 7.9 ng/mL) (38). However, 2 patients received WBRT, which may further contribute to accelerated TKI penetration of the BBB (15).

Moreover, in vitro studies using a panel of kinase domain mutations of EGFR in transfected cells determined varying IC50 values depending upon the type of activating mutations (39). For example, the IC50 for erlotinib for cells harboring a L858R mutation was 6 nmol/L suggesting that erlotinib in the CSF may be effective against these tumors.

Although for most NSCLC patients with brain metastases, WBRT is considered the first-line treatment option, emerging data suggest that erlotinib could represent a viable treatment option for this patient population. However, in view of the potential effect of WBRT on the BBB and penetration of erlotinib into the CSF, further studies are required to determine erlotinib concentrations in the CSF of NSCLC patients with brain metastases who are WBRT-naïve.

To date, the clinical data on erlotinib for the treatment of brain metastases of EGFR mutated tumors are very limited and are largely based on retrospective reports. In the study mentioned previously in 6 NSCLC patients with non-irradiated brain metastases, 4 of the tumors had an activating EGFR mutation (37). Following treatment with erlotinib 150 mg once daily, an ORR of 33.3% for metastatic brain lesions was achieved, increasing to 50% in patients with EGFR mutations (37). Moreover, several case reports have described some benefit of erlotinib treatment in brain metastases of EGFR mutated tumors with recurrence after WBRT (40, 41). Finally, in a retrospective analysis in 69 NSCLC patients with brain metastases, the ORR in 17 patients with EGFR mutations was 82.4%, with a median time to progression of 11.7 months (95% CI, 79–15.5) (7). Nine patients with EGFR mutations received standard WBRT prior to erlotinib treatment. Interestingly, in the remaining 8 patients with EGFR mutations, oral erlotinib was the sole treatment yielding an objective response in 6 cases (4 CR, 2 PR). In contrast, no responses were observed in the control group where EGFR mutations were not tested, even though they had all received WBRT.

Data from previous studies suggest that a higher CSF concentration can be achieved with erlotinib compared with gefitinib because of the higher peak plasma concentrations and higher BBB barrier permeability of erlotinib (13, 42). Although this could have possible implications for greater efficacy with erlotinib in the treatment of CNS metastases, particularly leptomeningeal metastases, this was not confirmed by the findings of a retrospective study (35). In another study, erlotinib was administered to 7 lung cancer patients who had developed CNS metastases following an initial good response to gefitinib for extra CNS lesions (43). Six of the patients had been locally pretreated with WBRT or radiosurgery before disease progression in the CNS. All patients were treated with erlotinib, which resulted in 3 PR and 3 SD. Neurologic symptoms improved in five of seven patients. In contrast, a single-institution, phase II study in 28 patients diagnosed with NSCLC harboring EGFR mutations and measurable CNS
metastases found no difference in PFS or OS according to the EGFR TKIs used (8). Six patients were treated with erlotinib, and 22 patients received gefitinib, depending on the physician’s choice. A PR was reported in 23 patients (83%) and 3 patients (11%) had SD. The median PFS and OS were 6.6 months (95% CI, 3.8-9.3 months) and 15.9 months (95% CI, 7.2-24.6 months), respectively.

Several attempts have been made to increase the efficacy of EGFR TKIs in NSCLC patients with CNS metastases (15). For example, as mentioned previously, the combination of EGFR TKIs and radiotherapy has potential synergistic effects at least partly due to “opening” of the BBB by radiation and radiosensitizing effects. In a prospective phase II study from two U.S. centers, 40 NSCLC patients with CNS metastases were treated with erlotinib (150 mg once daily) for 1 week and then concurrently with WBRT (2.5 Gy per day 5 days per week, to 35 Gy), followed by erlotinib maintenance (21). The ORR of CNS metastases was 86% (11 CR, 20 PR, 2 mixed responses, 1 SD). In 9 patients harboring EGFR mutations, the response rate was 89% (3 CR, 5 PR), and the median survival time was 19.1 months. Furthermore, the safety data were encouraging with no reports of neurotoxicity or grade ≥4 adverse events. Hence, this study contradicted earlier case reports raising safety concerns about the concurrent use of erlotinib during WBRT with particular attention to drug–drug interactions, neutropenic sepsis, and neurological status (44).

Another strategy to increase intracerebral efficacy is to boost the exposure of erlotinib in the CSF by increasing the administrated dose. Recently, Yu and colleagues reported the results from a phase I dose-escalation study evaluating twice-weekly pulse dose and low daily doses of erlotinib as first-line treatment for patients (n=34) with EGFR mutant lung cancers (45). Twelve patients (35%) had CNS disease at diagnosis with none of them developing progressive disease. A maximum tolerated dose (MTD) for erlotinib of 1,200 mg (days 1-2) and 50 mg (days 3-7) weekly was determined. The most frequent treatment-emergent adverse events were similar to those reported with standard doses of erlotinib. Sixteen patients were treated at the MTD and developed no treatment-related adverse events of grade ≥4, while 3 (19%) patients required a dose reduction of the pulse dose. Further studies are planned in NSCLC patients with brain metastases.

Afatinit. In the field of solid tumors, multi-targeted agents are promising contenders for the next generation of targeted therapies. Afatinib (Giotrif®, Boehringer-Ingelheim, Germany) is an oral irreversible TKI of all members of the EGFR family, which, as front-line therapy, has demonstrated promising efficacy compared with standard chemotherapy in the treatment of NSCLC patients with EGFR-positive mutations (e.g., del19, L858R) (reviewed by 46). In an analysis of 35 patients with stable brain metastases enrolled in the phase III LUX-Lung 3 trial, first-line treatment with afatinib was associated with a trend towards longer median PFS compared with first-line cisplatin/pemetrexed (11.1 vs. 5.4 months; hazard ratio 0.52; p=0.13) (47). In a more recently published study, the outcomes of TKI-pretreated NSCLC patients with brain metastases who received afatinib were reported (23). Brain metastases and/or leptomeningeal disease were documented in 100 patients and 74% of these had EGFR mutation. Following treatment with afatinib, the ORR (brain) was 35% and OS was 9.8 months (31% maturity). Notably, an afatinib CSF concentration of approximately 1 nM was reported in a female patient who experienced a marked improvement in performance status with a PR on afatinib therapy. Overall, information on the ability of afatinib to cross the BBB is currently limited; however, due to its potency at relatively low concentrations (IC_{50} for erbB1: 0.5 nM, erbB2: 14 nM, erbB4: 1 nM [23]) afatinib may remain effective in the CNS upfront or after resistance to other TKIs has developed. In contrast, erlotinib CSF levels of approximately 5% of plasma levels are considered adequate for receptor inhibition, while gefitinib levels of approximately 1% of plasma levels are considered inadequate for inhibition (48).

Anaplastic Lymphoma Kinase (ALK) TKIs

Anaplastic lymphoma kinase (ALK) gene rearrangements are present in 3-5% of patients with NSCLC and are closely associated with younger age, light/never smoking history, and adenocarcinoma histology (49). They have recently emerged as key drivers in cancer development and maintenance and have been shown to increase sensitivity to treatment with ALK TKIs including crizotinib, ceritinib, and alectinib (50). Interestingly, ALK gene rearrangements are relatively heterogeneous; in fact, at least 27 ALK fusion variants have now been described, the most common of which is an inversion in the short arm of chromosome 2 that juxtaposes the 5-end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3-end of the ALK gene, thus resulting in the EML4-ALK fusion tyrosine kinase (51). However, at the present time it is unclear whether a different sensitivity exists to ALK TKIs based on the specific type of the ALK fusion variant.

As reported in the PROFILE 1007 trial, metastatic involvement of the CNS appears to be a relatively common complication in patients with ALK-positive NSCLC, with approximately 35% of ALK-positive patients documented in 100 patients and 74% of these had EGFR mutation. Following treatment with afatinib, the ORR (brain) was 35% and OS was 9.8 months (31% maturity). Notably, an afatinib CSF concentration of approximately 1 nM was reported in a female patient who experienced a marked improvement in performance status with a PR on afatinib therapy. Overall, information on the ability of afatinib to cross the BBB is currently limited; however, due to its potency at relatively low concentrations (IC_{50} for erbB1: 0.5 nM, erbB2: 14 nM, erbB4: 1 nM [23]) afatinib may remain effective in the CNS upfront or after resistance to other TKIs has developed. In contrast, erlotinib CSF levels of approximately 5% of plasma levels are considered adequate for receptor inhibition, while gefitinib levels of approximately 1% of plasma levels are considered inadequate for inhibition (48).
Crizotinib. Crizotinib (Xalkori®, Pfizer, USA) is an oral small-molecule TKI targeting ALK, c-MET, and ROS1. It has achieved an objective response of 61% in ALK-positive NSCLC patients and a median PFS of 9.7 months (59). Crizotinib was superior to chemotherapy as second-line treatment for ALK-positive NSCLC, achieving a response rate and PFS similar to that reported in a phase I trial (52). However, despite such encouraging activity, all patients ultimately progress on crizotinib due to the emergence of bypass-mediated resistance pathways and second-site mutations. Although the aforementioned studies are flawed by their retrospective nature as well as by the fact that brain imaging was not routinely performed during follow-up of patients without brain metastases at baseline, they strongly suggest that the CNS represents a dominant site of progression in ALK-positive patients treated with crizotinib.

An important factor in the development of drug resistance is that of insufficient drug exposure, for example, within the CSF. A crizotinib CSF concentration <0.3% of that in plasma was reported in a male NSCLC patient treated with crizotinib 250 mg, consistent with the theory of low CNS penetration of crizotinib (53). Furthermore, Weickhardt et al. (61) reported the CNS to be the first site of progression in 13 of 28 patients (46%) with ALK-rearranged tumors treated with crizotinib. Also of note was the fact that most of these patients (11/13, 85%) were without coincident systemic progression (61).

More recently, a retrospective analysis of crizotinib-treated patients within the PROFILE 1005 and PROFILE 1007 trials found a 20% (51/253) incidence of new CNS lesions in patients without brain metastases at baseline and a 70.5% (69/98) incidence of CNS progression in patients with known brain metastases prior to crizotinib initiation (62). Although the aforementioned studies are flawed by their retrospective nature as well as by the fact that brain imaging was not routinely performed during follow-up of patients without brain metastases at baseline, they strongly suggest that the CNS represents a dominant site of progression in ALK-positive patients treated with crizotinib.

Ceritinib. Current options for overcoming drug resistance to crizotinib include treatment with the second-generation ALK inhibitors, ceritinib and alectinib. Ceritinib (Zykadia®, Novartis, Switzerland), an inhibitor of ALK- and insulin-like growth factor-1 receptor TKIs, achieved an ORR of 56% in NSCLC patients who had previously progressed on crizotinib (63). Ceritinib is orally available with a low IC₅₀ of 0.00015 mM (64). Apart from crizotinib, it has also been proposed that ceritinib may overcome resistance to other next-generation ALK inhibitors, such as alectinib (64).

The frequent development of brain metastases in patients with ALK-positive NSCLC significantly affects the oncology community’s ability to provide effective treatment for this patient population, particularly for those who have developed resistance to crizotinib. According to the study by Shaw et al. (63) the median PFS with a daily ceritinib dose ≥400 mg among 64 patients with brain metastases at baseline was similar to that among 50 patients without brain metastases (6.9 months vs. 7.0 months; p=0.37). In addition, the results of a phase I, single-arm study of ceritinib were updated by Kim et al. (55) at the 2014 American Society of Clinical Oncology Annual Meeting. Among 124 patients with initial brain metastases, use of ceritinib (750 mg daily) achieved an ORR of 54.0% (95% CI, 44.9%-63.0%) and a median PFS of 6.9 months (95% CI, 5.4-8.4). Tumor shrinkage was observed in 50.0% (95% CI, 39.7%-60.3%) of patients with brain metastases who had received a previous ALK inhibitor and 69.2% of brain metastases patients (95% CI, 48.2%-85.7%) who had not. Although these data are “immature,” the marked response to ceritinib is suggestive of a clinically meaningful effect on brain metastases in ALK-positive NSCLC.

Alectinib. Alectinib (Alecensa®, Chugai, Japan) is a second-generation, orally bioavailable small molecule inhibitor of ALK, with potent in vitro activity against both wild-type ALK (IC₅₀ 1.9 mmol/L) and mutated ALK, including mutations...
associated with crizotinib resistance (65). In ALK inhibitor-naive patients with ALK-rearranged NSCLC (n=46), alectinib achieved an ORR of 94% (65). Japan was the first country to approve alectinib for the treatment of ALK fusion gene-positive, recurrent or advanced NSCLC (66).

In a recently published phase I/II study, Gadgeel and colleagues (56) evaluated the efficacy of alectinib in patients with crizotinib-resistant ALK-rearranged NSCLC. Eleven of 21 patients (52%) with CNS metastases at baseline achieved an ORR, and 5 of 9 patients (56%) with measurable CNS lesions at baseline achieved a PR. Measurable CSF concentrations of alectinib were also reported in patients with paired CSF and plasma samples (5 patients, all with CNS metastases at baseline). The activity of alectinib in the patients with leptomeningeal carcinomatosis accords with favorable activity of alectinib on parenchymal CNS lesions and suggests that alectinib has the potential to address the high unmet medical need facing patients with leptomeningeal metastasis. Moreover, the clinical control in CNS disease reported with alectinib is supported by the relation between paired CSF and plasma concentrations. Although the dataset is limited, paired CSF and systemic plasma samples showed alectinib penetration of the CNS and support a linear relation between CSF and free alectinib concentrations in plasma.

It is anticipated that the ongoing phase II part of this trial investigating oral alectinib 600 mg twice daily will provide further insight into the systemic and CNS activity of this ALK inhibitor (55). In addition, a phase III randomized study is underway (NCT02075840) comparing alectinib with crizotinib in patients with treatment-naive, advanced ALK-rearranged NSCLC. The primary endpoint of the study is PFS and the secondary endpoint is time to CNS progression.

Most recently the efficacy of alectinib was evaluated in 138 ALK-positive NSCLC patients who had failed prior crizotinib (phase II study). For patients with baseline measurable CNS metastases (n=34) ORR was 55.9% (95% CI, 37.9%-72.8%) including 5 patients with a CR, and medium PFS was 10.3 months (56). Alectinib was well tolerated and demonstrated excellent intracranial activity. Similar results came from another group of researchers. Gandhi et al. (58) evaluated the efficacy of alectinib in ALK-positive NSCLC patients who had progressed on crizotinib in a US/Canadian population (phase II trial, n=87). In patients with measurable brain metastases at baseline (n=16) ORR was 68.8% (95% CI, 41.3%-89.0%). Two patients achieved a CR and the DCR was 100%. Based on the findings of both studies, a phase III trial of first-line alectinib versus crizotinib and an expanded-access program are ongoing (ALEX trial, NCT02075840).

At this time, available data from studies evaluating second-generation ALK inhibitors in patients with ALK-rearranged NSCLC suggest some degree of CNS activity with these agents; however, more studies, particularly trials that include larger numbers of patients with untreated brain metastases and measurable disease, are undoubtedly needed.

### Further Considerations

The management of patients with brain metastases continues to present a major challenge in oncology, with relatively low response rates and limited survival benefits achieved with current chemotherapeutic options. In a small subgroup of patients harboring EGFR-activating mutations or the ALK rearrangement, TKIs have been reported to improve clinical outcome. There is also evidence to suggest that initial treatment with the EGFR TKIs, gefitinib, erlotinib, and afatinib, is associated with a lower risk of progression of brain metastases in patients with EGFR mutation-positive NSCLC. However, isolated or pre-dominant progression of brain metastases is a major issue in patients on EGFR and ALK inhibitors, regardless of initial response to the therapy, due to relative drug underexposure in the brain. Targeted therapy with improved brain penetration is desired.

Data on the efficacy of TKIs in the treatment of NSCLC patients with brain metastases are currently limited; a major reason for this is the exclusion of patients with brain metastases from many phase III studies. There is also a noticeable absence of phase III studies comparing WBRT with EGFR or ALK TKI therapy, thereby precluding the ability to make any comparison between standard treatments (e.g., WBRT, chemotherapy). Further studies are required to address these shortcomings and
to provide definitive data to aid selection of the optimal sequence of TKI therapy and radiotherapy.

Notably, virtually all ALK TKIs with clinically available data, including crizotinib and next-generation drugs such as ceritinib and alectinib, have shown a considerable degree of activity against CNS metastases. However, these data should be interpreted cautiously as most data are derived from studies that were not specifically aimed at evaluating CNS response. Also, cross comparison among ALK TKIs is difficult, as these studies adopted different end-points for the assessment of CNS response as well as different criteria for the definition of measurable CNS lesions at baseline. In addition, the assessment of CNS response was not performed according to independent radiological review in all studies.

Finally, patient populations were not uniform as they differed based on several clinical characteristics such as type of prior treatment (pretreatment with an ALK TKI, prior brain radiotherapy) as well as type (e.g., meningeal carcinomatosis) and number of CNS lesions. However, despite such shortcomings there is a sufficient body of data to support a delay in brain radiotherapy in favor of therapy with an ALK TKI in patients with ALK-positive NSCLC and asymptomatic brain metastases. However, newer strategies are eagerly awaited for patients with ALK-positive NSCLC and intracranial disease progression.

Considered together, the available clinical data suggest that the EGFR and ALK TKIs will provide clinicians with a viable alternative treatment option for NSCLC patients with asymptomatic brain metastases, particularly those with *EGFR*-activating mutations or harboring *ALK* rearrangement. However, larger phase III studies are required to fully define the activity of these agents and their place in the therapeutic armamentarium of brain metastases. Data on the efficacy of other targeted therapies in NSCLC patients with brain metastases, including B-Raf inhibitors, *HER2* inhibitors, or *RET* inhibitors are lacking. As the list of validated targets is likely to grow in the near future, it will be vital to also address the issue of their systemic effect in subsets of patients with brain dissemination, with particular emphasis on drug pharmacokinetic and pharmacodynamic properties, as well as interaction with WBRT. The same questions should be answered for immune checkpoint inhibitors and cancer vaccines currently being tested in NSCLC patients.

**Conflicts of Interest**

Wolfram Dempke and Klaus Edvardsen are employees of AstraZeneca (UK). Shun Lu, Niels Reinmuth, Martin Reck, and Akira Inoue declare no conflicts of interest.

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Dempke et al: TKI Treatment for NSCLC Brain Metastases (Review)


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