



# Anaplastic lymphoma kinase inhibitor development: enhanced delivery to the central nervous system

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Anaplastic lymphoma kinase (ALK) gene rearrangement is a potent oncogenic driver in non-small cell lung cancer (NSCLC) and occurs in about 5% of patients with NSCLC (1). ALK-positive NSCLC is associated with a high risk of central nervous system (CNS) dissemination, and CNS metastases coexist in approximately 30% of patients with ALK-positive NSCLC at the time of diagnosis (2). Brain metastasis management aims to enhance survival and quality of life, with a maximum preference for neurocognitive function maintenance. Therefore, it is crucial to properly treat CNS and systemic lesions.

Brain cells are segregated from the entire body by several barriers, including the blood-brain barrier (BBB), blood-cerebrospinal fluid (CSF) barrier, blood-retinal barrier, and blood-spinal barrier (3,4). The BBB assists CNS homeostasis by preserving the CNS from poisonous substances (5). BBB active drug efflux transporters of the adenosine triphosphate (ATP)-binding cassette gene family, including the P-glycoprotein (P-gp), the multidrug resistance protein, and the breast cancer resistance protein (BCRP), are crucial for pharmacokinetics and effects of drugs (6-8). The effects of ATP-binding cassette (ABC) efflux transporters in the BBB include reducing the appearance of the neurotoxic adverse effects of drugs. In contrast, ABC efflux transporters may also restrict the central accumulation of drugs that are effective for treating

CNS metastasis (5). The BBB is localized at the endothelial cells comprising the brain microvessels. In opposition to the peripheral endothelial cells, the BBB endothelial cells possess tight junctions. Because the existence of a tight junction among adjoining endothelial cells obstructs the paracellular space at the BBB, the permeability of small molecular drugs depends on their transcellular transport across the BBB, which is mainly brought about by passive transport. Several key physicochemical parameters, including molecular weight, lipophilicity, polar surface area, hydrogen bonding, and charge, request optimization to enhance BBB permeability by passive transport (9).

Today, five ALK inhibitors, including crizotinib, ceritinib, brigatinib, alectinib, and lorlatinib, are available for clinical use. Ceritinib, brigatinib, alectinib, and lorlatinib have been designed to overcome the failure of crizotinib at the brain site. Second- and third-generation ALK tyrosine kinase inhibitors (TKIs) are used for ALK positive patients with brain metastases instead of chemotherapy and first-generation TKI (10). The second- and third-generation ALK inhibitors are ingeniously designed to cross BBB more efficiently than crizotinib and to achieve higher concentrations in the CSF, thus providing a superior ability to control the CNS extension. The effect was achieved by reducing their molecular weight, increasing lipophilicity, and changing the number of available hydrogen bond donors.

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**Table 1** Intracranial response in patients with measurable brain metastasis as per investigator assessment

Study arm	Intracranial metastasis and previously treatments	Intracranial overall response rate (95% CI)
Arm 1 (n=28)	Brain RT (+)/ALK I (+)	39.3 (21.5–59.4)
Arm 2 (n=29)	Brain RT (-)/ALK I (+)	27.6 (12.7–47.2)
Arm 3 (n=7)	Brain RT (+)/ALK I (-)	28.6 (3.7–71.0)
Arm 4 (n=33)	Brain RT (-)/ALK I (-)	51.5 (33.5–69.2)
Arm 5 (n=8)	Leptomeningeal meta	12.5 (0.3–52.7)

RT, radiotherapy; ALK I, anaplastic lymphoma kinase inhibitor; CI, confidence interval.

**Table 2** Blood-brain barrier penetration

ALK inhibitor	Concentration ratio	CSF concentration (ng/mL)
CSF to unbound (free) plasma		
Ceritinib	13–35% (14)	2.31–12.4
Alectinib	86% (20)	1.396
Lorlatinib	75–77% (21,22)	2.64–125
CSF to serum/plasma		
Crizotinib	0.06–0.26% (23,24)	0.35–0.616
Brigatinib	1.27% (25)	13.23

ALK, anaplastic lymphoma kinase; CSF, cerebrospinal fluid.

Ceritinib is a second-generation ALK TKI, and in a murine experiment, the blood-to-brain transition ratio of ceritinib reached 15% (11). In the phase I trial (ASCEND-1), ceritinib showed overall intracranial response rates of 36% and 63% with and without ALK TKI pretreatment, respectively (12). In the ASCEND-2 study, the intracranial response rate reached almost 40%, and the intracranial disease control rate was 85% (11). The phase 3 ASCEND-4 trial compared ceritinib with chemotherapy as a first-line treatment, and in patients with CNS metastases, the mean progression-free survival was 10.7 months in the ceritinib group and 6.7 months in the chemotherapy group (13). The ASCEND-7 study was conducted to further assess ceritinib efficacy and safety in ALK-positive patients having brain and leptomeningeal metastases. In the issue of *Clinical Cancer Research*, Chow *et al.* (14) reported the phase 2 ASCEND-7 trial results. The trial investigated patients with ALK-positive NSCLC examined by the FDA-approved Vysis ALK Break Apart FISH Probe Kit test. ASCEND-7 was one of the prospective trials designed to

use uniform eligibility criteria and assessments to investigate intra/extracranial effects of an ALK-targeted drug, although ASCEND-7 included a relatively small number of patients. Patients with active brain metastases were allocated to study arms 1–4 according to prior brain radiation and/or prior exposure to an ALK inhibitor (arm 1: prior radiotherapy/ALK inhibitor-pretreated; arm 2: no radiotherapy/ALK inhibitor-pretreated; arm 3: prior radiotherapy/no ALK inhibitor; arm 4: no radiotherapy/no ALK inhibitor). Patients with leptomeningeal carcinomatosis were evaluated in arm 5. Intracranial overall response rates per investigator assessment were 39.3% [95% confidence interval (CI): 21.5–59.4] in arm 1, 27.6% (95% CI: 12.7–47.2) in arm 2, 28.6% (95% CI: 3.7–71.0) in arm 3, and 51.5% (95% CI: 33.5–69.2) in arm 4. In arm 5, the intracranial response was 12.5% (95% CI: 0.3–52.7) (*Table 1*). Paired CSF and plasma sampling showed that ceritinib passed through the human BBB. Paired samples from 3 patients showed that ceritinib passed through the human BBB with a CSF-to-plasma concentration ratio of 13–35% (14). In a recent study, Katayama *et al.* (15) reported that ceritinib is a P-gp substrate, and P-gp inhibition reverses ceritinib and crizotinib resistance. Furthermore, Kort *et al.* (16) reported that P-gp and BCRP limit brain accumulation of ceritinib.

In brain metastases, the BBB is impaired and is shown to be different from the normal healthy BBB (17–19). The extent of BBB impairment is a key factor that affects the entry of drugs into the CNS. Effective therapy requires attaining targetable drug concentrations in the CNS. So, effective therapy of brain lesions requires efficient drug delivery across the BBB. Some clinical studies have reported on brain and CNS penetration of ALK inhibitors, although the conclusions from the small number of cases must be interpreted with caution. Usually, surrogate endpoints such as CSF-to-plasma ratios are substituted to consider whether a drug can be transported into the CNS and pass through the BBB (*Table 2*). Paired samples showed that ceritinib passed through the human BBB with a CSF-to-plasma concentration ratio of 13–35% (14). Another second-generation tyrosine kinase inhibitor, alectinib, showed a penetration rate of 86% into the CSF (20). Lorlatinib is a highly potent, selective, third-generation ALK inhibitor specifically developed to pass through the BBB and has broad ALK mutational coverage. This was confirmed in clinical trial, where the mean CSF-to-plasma ratio (unbound) was 0.75 in four patients with matched specimens available (21). Additionally, Sun *et al.* reported that the regression analysis based on a sample

of 5 patients with available CSF and estimated unbound plasma concentration data indicated a CSF-to-free plasma concentration ratio of 0.77 (22). Although the many CNS adverse events of lorlatinib, including mood, cognitive, speech, and psychotic effects, resolved without intervention or with lorlatinib dose modification and/or concomitant medication, the toxicity profile of lorlatinib may make the physicians hesitant providing it as first-line therapy.

Next-generation ALK inhibitors which are effective for brain metastases should be considered first-line therapy for patients with asymptomatic brain metastases. Radiotherapy or surgical resection may be considered in patients with symptomatic brain metastases. It is encountering a paradigm evolution from cranial radiotherapy to the use of more potent and central nervous system-penetrating ALK inhibitors. Our goal of treatment is to avert or postpone radiation therapy and its cognitive sequelae in ALK patients. The intracranial effects of novel TKIs may also potentially turn patients from requiring whole-brain radiotherapy to stereotactic radiosurgery with lighter side effects. A network meta-analysis demonstrated that lorlatinib had superior efficacy for patients with brain lesions but exhibited unique side effects. However, alectinib showed superior efficacy and lower toxicity in patients with ALK-positive NSCLC. On the other hand, ALTA trials demonstrated up to 70% response of ALK patients with brain metastasis, so brigatinib might be able to reverse the activation of a greater percentage of brain-related metastasis effectors despite relatively lower blood-brain barrier penetration (26). Treatment with second-generation ALK inhibitors, such as alectinib, brigatinib, ceritinib, and ensartinib, significantly improved overall survival compared with crizotinib (13). Much remains to optimize outcomes for patients with ALK CNS diseases. According to the concept of using the most effective drug first, the choice of the first line treatment for advanced ALK-positive NSCLC with CNS involvement is still under debate, and ceritinib's place in the landscape of ALK-positive NSCLC will need to be defined.

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