



Crizotinib for *ALK* rearrangement-positive non-small cell lung cancer patients with central nervous system metastasis

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Patients with central nervous system (CNS) metastases in general experience have a deterioration in performance status and a limited survival time (1). CNS metastasis of non-small cell lung cancer (NSCLC) has been the subject of renewed interest of late given that small-molecule tyrosine kinase inhibitors (TKIs), such as those that target activated forms of the epidermal growth factor receptor (EGFR), have the potential to improve local tumor control in molecularly selected individuals. Given that the concentration of EGFR-TKIs is much lower in cerebrospinal fluid (CSF) than in plasma, however, frequent isolated CNS metastasis, without other systemic progression, has been detected in patients with advanced NSCLC who show a response to these drugs (2). Similar concerns have also been raised for patients with NSCLC positive for the *EML4-ALK* fusion gene treated with the anaplastic lymphoma kinase (ALK)-targeted TKI crizotinib.

While the need for randomized phase III trials comparing targeted therapy to standard cytotoxic chemotherapy in patients with low-frequency driver mutations such as *ALK* rearrangements has been under discussion, a randomized phase III study (PROFILE 1014) recently demonstrated a superior progression-free survival (PFS), objective response rate, and patient-reported outcomes for crizotinib versus pemetrexed-platinum combination chemotherapy in *ALK* rearrangement-positive NSCLC patients (3). Focusing on the intracranial efficacy of crizotinib in such patients enrolled in the PROFILE 1014 study, Solomon *et al.* have now reported that PFS was significantly longer with crizotinib versus chemotherapy for individuals with stable

treated brain metastases (4). Intracranial time to tumor progression also tended to be longer on crizotinib compared with chemotherapy, although this difference did not achieve statistical significance. Intracranial progression—worsening of existing or development of new intracranial lesions—is often the first manifestation of disease progression in patients treated with crizotinib, and intracranial disease progression as the sole site of progression during crizotinib treatment was more frequent in patients with stable treated brain metastases (38%) than in those without known brain metastases (19%). The management of patients who show recurrent isolated CNS failure during crizotinib therapy is thus an emerging clinical problem.

A case study found that the concentration of crizotinib is much lower in CSF than in plasma (5), suggesting that the likelihood of isolated CNS metastasis is greater than that of disease progression elsewhere in patients with *ALK* rearrangement-positive advanced NSCLC who are treated with crizotinib. Systemic disease progression (also known as acquired resistance) in patients receiving crizotinib occurs through several molecular mechanisms including the acquisition of a mutation at the so-called gatekeeper site in the tyrosine kinase domain of ALK, and activation of bypass pathways (6,7). In contrast, extracranial tumors in patients who experience isolated CNS metastasis as a result of poor drug penetration through the blood-brain barrier (pharmacokinetic resistance) are likely to remain sensitive to the corresponding molecularly targeted therapy. We have previously shown that the resumption of daily administration of crizotinib after whole-brain radiotherapy or stereotaxic radiotherapy for isolated CNS failure in

NSCLC patients was found to be effective for control of extracranial disease (8). Although the molecular mechanisms of resistance to crizotinib operative in the new study of Solomon *et al.* (4) were not determined by analysis of tissue or CSF samples, most patients who developed isolated intracranial progressive disease during crizotinib treatment received crizotinib for >3 weeks beyond disease progression at the discretion of the treating physician, suggesting that most physicians may consider crizotinib beyond intracranial disease progression to be beneficial.

Novel strategies to enhance exposure of the CNS to ALK inhibitors, including the development of new drugs with a greater ability to cross the blood-brain barrier, are thus warranted. Alectinib is a second-generation, ALK-selective TKI with more potent inhibitory activity toward ALK (9). In animal models, alectinib generates relatively high brain/plasma concentration ratios, ranging from 0.63 to 0.94 (10). Clinically, an objective response was achieved in 48% of *ALK* rearrangement-positive, crizotinib-resistant NSCLC patients treated with alectinib at 600 mg twice daily in a phase II trial (11). Importantly, 75% of patients with measurable CNS lesions at baseline achieved an intracranial response. The J-ALEX study, a randomized phase III trial comparing the efficacy of alectinib (300 mg twice daily) with that of crizotinib (250 mg twice daily) in Japanese patients with *ALK* rearrangement-positive NSCLC, found that alectinib reduced the risk of disease worsening or death (PFS) by 66% compared with crizotinib (hazard ratio of 0.34, with a 99% confidence interval of 0.17 to 0.70; $P < 0.0001$) (12). Of note, the allowed dose of alectinib in Japan is lower than that in the United States, which allows alectinib to be administered at 600 mg twice daily. The global randomized phase III study ALEX (NCT02075840) comparing alectinib (600 mg twice daily) with crizotinib (250 mg twice daily) in treatment-naïve patients with *ALK* rearrangement-positive advanced NSCLC is ongoing. Whether alectinib therapy reduces the risk of CNS progression compared with crizotinib remains unknown, but current evidence suggests that alectinib may prevent or delay the emergence of CNS metastases.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. *J Clin Oncol* 2005;23:6207-19.
2. Lee YJ, Choi HJ, Kim SK, et al. Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with nonsmall-cell lung cancer. *Cancer* 2010;116:1336-43.
3. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167-77.
4. Solomon BJ, Cappuzzo F, Felip E, et al. Intracranial Efficacy of Crizotinib Versus Chemotherapy in Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer: Results From PROFILE 1014. *J Clin Oncol* 2016;34:2858-65.
5. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 2011;29:e443-5.
6. Tanizaki J, Okamoto I, Okabe T, et al. Activation of HER family signaling as a mechanism of acquired resistance to ALK inhibitors in EML4-ALK-positive non-small cell lung cancer. *Clin Cancer Res* 2012;18:6219-26.

7. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci Transl Med* 2012;4:120ra17.
8. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol* 2013;8:654-7.
9. Sakamoto H, Tsukaguchi T, Hiroshima S, et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. *Cancer Cell* 2011;19:679-90.
10. Kodama T, Hasegawa M, Takahashi K, et al. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol* 2014;74:1023-8.
11. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol* 2016;17:234-42.
12. Nokihara H, Hida T, Kondo M, et al. Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive ALK-positive non-small cell lung cancer (ALK+ NSCLC): Primary results from the J-ALEX study. *J Clin Oncol* 2016;34:abstr 9008.

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