Commentary

Alectinib for the management of ALK-positive non-small cell lung cancer brain metastases

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Anaplastic lymphoma kinase (*ALK*) rearrangements were first identified as an oncogenic driver in non-small cell lung cancers (NSCLC) in 2007, specifically the gene rearrangement between ALK and *echinoderm microtubule-associated protein like 4* (*EML4*) (1). *ALK* rearrangements occur in 3–5% of NSCLC patients and have been shown to be associated with younger age, never-smokers, advanced clinical stage, and adenocarcinoma with signet ring cells (2-4). Just 3 years later in 2010, a phase I/II trial of the small molecule tyrosine kinase inhibitor crizotinib demonstrated an overall response rate of 57% in patients with ALK-positive advanced NSCLC with mild side effects (5), prompting approval by the United States Food and Drug Administration (FDA) in 2011. In 2014, the phase 3 trial PROFILE 1014 showed crizotinib was superior to standard first-line pemetrexed and platinum chemotherapy in patients with previously untreated advanced ALK-positive non-squamous NSCLC with an overall response rate of 74% (6).

Despite these promising results for crizotinib response, most patients ultimately experience disease progression within 1 year (6). The central nervous system (CNS) has been reported to be the most common site of progression for patients on crizotinib, occurring in 70% of patients with known brain metastases and developing in 20% of patients without pre-existing brain metastases (7). Of note, as many as 30% of patients with ALK-positive NSCLC are found to have brain metastases at time of lung cancer diagnosis (8). As crizotinib has been to shown to have poor blood-brain barrier penetration (9), the second-generation ALK inhibitor alectinib has emerged as an attractive agent to treat both systemic and intracranial disease in ALK-positive NSCLC. Alectinib was approved by the FDA in 2015 for patients with ALK-positive NSCLC who have failed crizotinib, based on phase II clinical trials demonstrating objective response rates of 50–52% (3,10). Pre-clinical studies have demonstrated that alectinib has a high penetration in the brain and is not transported by the P-glycoprotein efflux transporter, which is a key factor for maintaining the blood-brain barrier (11). In an *in vivo* mouse model of EML4-ALK lung adenocarcinoma, alectinib showed efficacy in pleural carcinomatosis, bone, and brain metastases, while crizotinib only showed efficacy in pleural carcinomatosis and bone and not in brain (12). A clinical phase 1/2 study (AF-002JG) of alectinib in 47 patients with crizotinib-resistant ALK-positive NSCLC showed no progression of CNS metastases (13).

Gadgeel *et al*. have now presented a pooled analysis of CNS response to alectinib from two studies of pre-treated patients with ALK-positive NSCLC, NP28673 and NP28761 (14). These were phase 2 trials investigating efficacy and safety of alectinib in patients with crizotinib-refractory ALK-positive NSCLC (3,10). The pooled analysis by Gadgeel *et al*. included 136 total patients who had baseline CNS disease, and CNS response endpoints

were assessed in two populations: patients with measurable CNS disease at baseline and patients with measurable and/or non-measurable CNS disease at baseline. Fifty patients had measurable CNS disease at baseline, while 86 patients had non-measurable disease at baseline. Patients who previously received whole brain radiation or stereotactic radiosurgery were included (70%). For patients with measurable CNS disease at baseline, the CNS objective response rate was 64%, with complete response in 22%. For patients with measurable and/or non-measurable CNS disease at baseline, the CNS objective response rate was 43%, with complete response in 27%. The CNS objective response rate was 36% for patients who received prior radiation and 59% for patients without prior radiation. Overall, the authors suggest that alectinib may be an attractive and perhaps preferable alternative to brain radiation for CNS progression in these patients, on the basis of promising efficacy and the avoidance of certain radiation-related toxicities.

One important consideration when interpreting this analysis is the inherent limitation of the standard RECIST criteria for the measurement of baseline CNS disease and response. This cannot account for potential pseudoprogression which can be seen from radiation necrosis following radiation, for example, and a high number of patients in the pooled analysis received prior intracranial radiotherapy. A patient in AF-002JG developed CNS progression according to RECIST criteria with 40% enlargement of a tumor previously treated with stereotactic radiation with subsequent surgical resection demonstrating radiation necrosis with no viable tumor (13). Similarly, Ou *et al*. reported two cases of pseudoprogression from radiation necrosis during alectinib treatment, confirmed by surgical pathology, which met RECIST criteria for progressive disease (15). While surgical resection of all enlarging lesions is not feasible to confirm viable tumor, the advancement of diagnostic tests such as magnetic imaging spectroscopy or perfusion imaging, positron emission tomography, or temporal observation with steroid challenge may offer more insight and allow for better characterization of CNS progression versus pseudoprogression (16).

While the CNS response to alectinib published in the pooled analysis is encouraging, one may also consider data that demonstrates discordance in genetic alterations in brain metastases compared to primary tumors (17). This suggests that molecular testing should be performed on brain metastasis tissue or cerebrospinal fluid, when available, to maximize opportunities to deliver appropriate targeted therapies. Additionally, it has been proposed that brain metastases may not develop secondary resistance mutations to targeted therapies that occur in other systemic tumors due to reduced drug penetration of the blood-brain barrier (18).

If a patient has isolated progression in the brain but otherwise maintains systemic response to targeted therapy, durable intracranial control can be obtained with local therapy such as stereotactic radiosurgery, and the patient may be best served by continuing the same targeted therapy as long as extracranial disease control is maintained. Local therapy such as whole brain radiation or stereotactic radiosurgery remains the standard of care for progressive brain metastases, particularly when symptomatic (note that patients with symptomatic CNS disease were specifically excluded from these protocols). The promising CNS activity of new targeted agents such as alectinib suggests that switching targeted agents may become a reasonable alternative to local therapy, but prospective data would ideally be needed to determine which strategy (i.e., alectinib *vs.* brain radiation) would offer the best survival, intracranial control, and therapeutic ratio for such patients. Combining targeted agents such as alectinib with brain radiation presents another potential avenue for maximizing intracranial control, and prospective data would be necessary in this scenario as well.

In summary, Gadgeel *et al*. reported good CNS response to alectinib in a pooled analysis from two studies of patients with crizotinib-resistant ALK-positive NSCLC. As the brain has previously been considered a sanctuary site from systemic antitumor drug agents, the preclinical and clinical data demonstrating CNS response to alectinib offers the promise of an effective new therapy to treat brain metastases in ALK-positive NSCLC, which are a significant contributor to morbidity and mortality for these patients. Future questions include optimal timing of ALK inhibitors compared to local modalities such as surgery and radiotherapy, and CNS response to alectinib in crizotinib-naïve patients.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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