Commentary

Alectinib—a new chapter in the management of *ALK*-positive lung cancer

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Discovered in lung cancer in 2007, anaplastic lymphoma kinase (*ALK*) rearrangements have emerged as important therapeutic targets in non-small cell lung cancer (NSCLC) (1). Like epidermal growth factor receptor (*EGFR*) mutations, *ALK* rearrangements define a distinct molecular subset of NSCLC and confer sensitivity to treatment with genotype-specific tyrosine kinase inhibitors (TKIs) (2). The first ALK inhibitor to enter the clinic was crizotinib (3). In randomized phase III trials, crizotinib produced significant improvements in objective response rates (ORRs) and progression-free survival (PFS) compared to first- and second-line cytotoxic chemotherapy (4,5). This has established crizotinib as a standard of care for the management of *ALK*-positive NSCLC. Nonetheless, patients almost invariably relapse on crizotinib—commonly within one year.

To combat the clinical challenge of crizotinib resistance, a number of more potent and structurally distinct, next-generation ALK inhibitors have been developed. Alectinib is one such highly-selective and potent, next-generation ALK inhibitor that has demonstrated significant anti-tumor activity against *ALK*-rearranged NSCLC in phase I trials (6,7). Recently, Shaw and colleagues reported a single-arm, phase II trial (NP28761) evaluating alectinib in patients with advanced, *ALK*-positive NSCLC previously treated with crizotinib (8). Conducted in the United States and Canada, NP28761 enrolled 87 *ALK*-positive patients, a majority of whom (74%) had also been previously treated with chemotherapy. Among 69 patients with measurable disease at baseline, objective responses were observed in 33 (ORR 48%). With a median follow-up duration of 9.9 months, the estimated median PFS and duration of response (DOR) were 8.1 months [95% confidence interval (CI), 6.2–12.6 months] and 13.5 months [95% CI, 6.7 months to not reached (NR)], respectively.

The study by Shaw *et al*. (8) is on the heels of a recent global phase II study of alectinib published by Ou and colleagues (NP28673) (9); the latter evaluated the safety and activity of alectinib within a cohort of 138 crizotinib-resistant, *ALK*-positive lung cancer patients. Among 122 patients with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), the ORR on alectinib was 50%, including an ORR of 45% among those patients previously treated with crizotinb and chemotherapy. Importantly, and similar to the NP28761 study above, the median PFS on alectinib in the global study was 8.9 months (95% CI, 5.6–11.3 months), including a median PFS of 13.0 months (95% CI, 5.5 months to NR) among chemotherapy-naive patients.

Collectively, the NP28761 and NP28673 studies are important for several reasons. First, together with an initial dose-finding study of alectinib (6), they helped form the basis for the recent regulatory approval of alectinib in the United Sates. Specifically, alectinib is now approved for the management of *ALK*-rearranged lung cancer previously treated with crizotinib. This serves to expand the armamentarium for *ALK*-positive NSCLC. Second, the significant antitumor activity of alectinib in the above studies reinforces the notion that *ALK*-positive lung cancers remain ALK-dependent following treatment and progression on crizotinib, and that these tumors are still susceptible to ALK-direct therapies. Third, these studies may be paradigm-changing in how clinicians approach the management of brain metastases in patients with *ALK*-positive lung cancer.

The central nervous system (CNS) has emerged as an important site of disease in *ALK*-positive lung cancer.

Indeed, various sites along the neuro-axis can be affected, including the brain parenchyma, leptomeninges, and/or the spinal cord itself (10). Among patients with newly diagnosed metastatic disease, brain metastases have been reported in nearly 30% of *ALK*-positive patients (4). While crizotinib has been associated with modest intracranial disease control (11), the CNS is also the most common site of relapse on crizotinib (12). This has generally been attributed to relatively poor penetration of crizotinib into the CNS (13).

Preclinically, alectinib produces high CNS-to-plasma ratios and impressive intracranial disease activity in animal models (14). In the NP28761 and NP28673 studies, brain metastases were present at study entry in approximately 60% of crizotinib-resistant patients (8,9). Impressively, among patients with measurable intracranial metastases at baseline, the intracranial ORRs in these studies were 75% (8) and 57% (9), respectively. High intracranial response rates were also observed in patients with no prior history of CNS-directed radiation therapy. It should be noted that for patients without measurable CNS lesions, only complete resolution of all lesions is considered a response. When including patients with both measurable and non-measurable CNS lesions, Shaw *et al*. reported an intracranial ORR of 40% (8), while Ou and colleagues reported an intracranial ORR of 42.9% (9). Beyond the intracranial activity described in the NP28761 and NP28673 studies, other investigators have described significant clinical and radiographic responses to alectinib in *ALK*-positive patients with leptomeningeal disease (15,16). Together, such findings establish alectinib as a potent, CNS-penetrable ALK inhibitor and raise important questions regarding the optimal management approach for *ALK*-positive patients with brain metastases moving forward.

Historically, management of CNS metastases in NSCLC has centered on the use of local therapies, such as surgical resection, whole-brain radiation therapy (WBRT), and/or stereotactic radiosurgery (SRS). However, such techniques, particularly WBRT, can be associated with significant morbidity, including late neuro-toxicity (17). Avoidance of such toxicity is becoming increasingly important as the median overall survival for *ALK*-positive patients with brain metastases is now greater than four years based upon one recent series (18). The high intracranial response rates in *ALK*-positive patients treated with alectinib suggests that such local therapies may be able to be deferred in some patients in favor of medical therapy. Moving forward, clinical trials of ALK inhibitors should incorporate careful, prospective evaluations and definitions of CNS anti-tumor activity in order to better characterize which populations are most likely to benefit from targeted therapy versus local-therapies for CNS metastases.

More broadly, the activity of alectinib raises important questions regarding the optimal selection of ALK inhibitors in the crizotinib-resistant setting. At least seven different next-generation ALK inhibitors are currently in clinical development (19). Both ceritinib and alectinib are now approved in the United States for this indication, and brigatinib has received breakthrough therapy designation by the U.S. FDA. Thus far, clinical trials directly comparing next-generation ALK inhibitors have not been performed, and cross-trial comparisons across agents should generally be viewed with caution. Nonetheless, three key factors may differentiate these next-generation ALK inhibitors over time: (I) CNS activity; (II) spectrum of activity against *ALK* resistance mutations; (III) and toxicity profiles.

As detailed above, alectinib has been associated with intracranial ORRs of 52–75% (6,8,9). By contrast, in a recent retrospective analysis of ALK-positive patients with measurable brain metastases who were treated with ceritinib on the phase I ASCEND-1 study, the intracranial ORR was 29.2% (20). Beyond CNS activity, next-generation ALK inhibitors have also demonstrated slightly different spectrums of activity against *ALK* resistance mutations in preclinical models (21-23). Thus, the presence or absence of specific *ALK* resistance mutations may guide selection of next-generation ALK inhibitors in the future. Finally, another key factor is the toxicity profiles of these agents. In the NP28761 and NP28673 studies evaluating alectinib, the most common adverse events (AEs) of any grade were constipation (33–36%), fatigue (26–33%), myalgia (23–24%) and peripheral edema (23–25%), but these were mostly grade 1–2 (8,9). In the North American study (NP28761), 16% of patients required alectinib dose reduction (8), while 21% required dose reduction/interruption in the global phase II study (NP28673) (9); conversely, in the phase I study of ceritinib, more than half of patients (62%) receiving 750 mg once daily (the current FDA-approved dose) required dose reduction (24). Ceritinib was also associated with high rates of gastrointestinal toxicity, including nausea (82%), vomiting (65%), and diarrhea (75%). Moreover, among patients receiving ceritinib, grade 3 ALT and AST elevations were observed in 21% and 11%, respectively.

In summary, the field of *ALK*-positive lung cancer has been one of the great success stories in the era of targeted therapies. In less than one decade from the initial discovery

of *ALK* rearrangements in NSCLC, we now have three targeted therapy agents that have received regulatory approval by the U.S. FDA. Nonetheless, the next set of challenges will be to conduct comparative studies across ALK inhibitors to determine the optimal selection and sequencing of such agents. One such study, the ALEX study, is now ongoing. This phase III study randomizes treatment-naive, *ALK*-positive NSCLC patients to receive either alectinib or crizotinib (NCT02075840). This study has completed enrollment and we eagerly await the final results. In parallel, translational research efforts will be vital to gain a deeper understanding of the mechanisms of resistance to next-generation ALK inhibitors, and how such resistance may affect sequencing in the clinic.

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Footnote

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