Editorial

# Second-generation anaplastic lymphoma kinase inhibitors: revolutionary or evolutionary?

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Since the discovery of anaplastic lymphoma kinase (*ALK*) rearrangement in non-small cell lung cancer (NSCLC) in 2007 (1), crizotinib was developed as the first targeted therapy for patients with advanced or metastatic *ALK*-positive NSCLC (2). However, even though the dramatic and rapid response, most patients experienced disease progression within one year after commencement of crizotinib (3,4). To overcome crizotinib resistance, many next-generation ALK inhibitors have been developed.

Shaw *et al*. published a phase I data of ceritinib, ASCEND-1 in 2014, in which the overall response rate (ORR) and median progression-free survival (PFS) was 58% and 7.0 months, respectively (5). Also, it showed an equivalent response rate of 56% in crizotinib-resistant NSCLC. Kim *et al*. published recently the updated analysis of ASCEND-1 that the ORR and median PFS was 72% and 18.4 months in ALK inhibitor-naive patients and 56% and 6.9 months in ALK inhibitor-pretreated patients, respectively. Of more interest, intracranial disease control was achieved in 79% of ALK inhibitor-naive patients and 65% of ALK inhibitor-pretreated patients. The intracranial responses were similar regardless of prior brain radiotherapy (6). Shaw *et al*. also published the phase II of alectinib, another 2$^{nd}$-generation ALK inhibitor, with an ORR of 48% in 2016 which seemed rather inferior to that of 93.5% in Seto *et al*.'s first report in 2013 (7,8). Intracranial response was observed in 55.9% (7). In addition, many other 2$^{nd}$-generation or even next-generation ALK inhibitors, such as brigatinib or lorlatinib, are now under clinical investigation.

As a result of the promising outcomes of 2$^{nd}$-generation ALK inhibitors, we might come up with several important questions. First, in a patient who shows disease progression on crizotinib, we wonder which next-generation ALK inhibitor should be given. The answer to this question is very difficult because many things might be considered. The pattern of relapse or progression varies from patient to patient. i.e., intracranial disease only, oligometastases and so on. The biological resistance mechanism might also vary from tumor to tumor. Safety or toxicity profile might be also different. For example, the most common adverse events for ceritinib were diarrhea (86%), nausea (83%) and vomiting (61%) while those for alectinib were fatigue (30%), myalgia (17%) and peripheral edema (17%). The most common grade 3 or 4 adverse events were diarrhea (6%), nausea (6%) and vomiting (4%) and fatigue (5%) during ceritinib treatment but peripheral edema (2%), and rash (2%) during alectinib treatment (6,9). So far, the outcomes of 2$^{nd}$-generation ALK inhibitors seem similar or comparable, but however, because of no randomized head-to-head trials comparing different ALK inhibitors, we have to interpret the data of each study very cautiously and to choose a next-generation ALK inhibitor individually for each patient based on pattern of disease progression, safety profile and if possible, biological mechanism. Focusing on brain metastases, the studies suggest that ceritinib and alectinib is highly effective in patients with brain metastases regardless of prior radiotherapy history (5-9). The NCI ALK Master protocol is undergoing to evaluate different next-generation ALK inhibitors with crizotinib (10).

The second question is whether this next generation ALK inhibitor can replace crizotinib as first-line therapy. At present, sequential therapy with crizotinib followed by a next-generation ALK inhibitor is a standard therapy. However, the median PFS of crizotinib was 10.9 months

in a randomized phase III study and the median PFS of ceritinib in ALK inhibitor pretreated patients is 6.9 months while the median PFS of ceritinib in ALK inhibitor-naive patients is 18.4 months (4,6). The first-line use of ceritinib seems comparable although whether this kind approach can lead to a comparable outcome is not yet known. This is another reason why we have to wait for results of the NCI ALK master protocol (10).

The third question is related to resistance mechanisms of each ALK inhibitor. Acquired crizotinib resistance develops in two ways; pharmacological or biological mechanism. Pharmacological resistance is due to inadequate drug availability or low CNS penetration, i.e., brain metastases or carcinomatosis meningitis. As mentioned above, the 2$^{nd}$-generation inhibitors showed good responses for the CNS metastases. Biological resistance can be categorized into two types; ALK dominant and ALK non-dominant. The one, accounting for about one third of the cases, involves either ALK fusion gene amplification or secondary mutation in ALK tyrosine kinase domain, which sterically interferes with the ability of the drug to bind and block the tyrosine kinase domain. The most frequent mutations are L1196M mutation followed by the G1269A mutation while the other known secondary mutations in crizotinib-resistant patients are 1151T-ins, L1152R, C1156Y, G1202R, and S1206Y (11-13). In a panel of engineered cancer cells driven by one of the nine different crizotinib-resistance ALK mutations, ceritinib has potent antigrowth efficacy in cells expressing L1196M, G1269A, S1206Y, and I1171T mutations while it does not in C1156Y, G1202R, 1151T-ins, L1152R, and F1174C mutations (14). Some tumors from the patients with acquired resistance to ceritinib were reported to have G1202R or F1174C/V mutation (14). Interestingly, resistance to alectinib may occur due to I1171 residue, against which ceritinib has been reported to have activity (15,16). There are also data supporting the sequential use of alectinib after ceritinib in patients harboring ceritinib resistance mutation F1174V (16). Of more interest, both ceritinib- and alectinib-resistant mutation G1202R can be managed with lorlatinib (17). These suggest that guided sequential use of ALK inhibitors be the appropriate approach based on serial molecular genotyping for not only resistant tumors but also untreated sensitive tumors. However, the other resistance mechanism to crizotinib is ALK non-dominant which is secondary to activation of alternative escape or bypass pathways, including IGF-1R, EGFR, KIT, c-MET, KRAS, and mTOR pathways (10-14). It accounts for one-third of crizotinib-resistant cases and can be overcome by combination therapies. To make the matter worse, the resistance mechanism in the remaining one third of the cases are not elucidated well so far. Resistance driven by an ALK-dominant mechanism can be overcome by a second-generation or next-generation ALK inhibitor but it is the case in only one third of resistance. The third question is what mechanism involves in development of ceritinib or alectinib or even other ALK inhibitors-resistance. Is the mechanism of ceritinib-resistance the same to that in crizotinib research? Does each mechanism have the same significance? Will we be able to get generalizable knowledge from research of ALK inhibitors? Finally, we come up with subsequent question what is the most appropriate approach for each resistant tumor. Research looking into the molecular basis of each resistance mechanism can lead to develop more effective therapeutic strategies. Identification of resistance mechanism in each tumor can guide more appropriate therapies which include sequential use of ALK inhibitors or combination of ALK inhibitor with targeted agents or chemotherapies or immune checkpoint inhibitors.

The development of ALK inhibitors from discovery of ALK translocation was a revolutionary event in the history of cancer treatment, changing the treatment paradigms to precision cancer medicine. Now, ALK inhibitor is evolving to be more effective in ALK-positive NSCLC. However, there are still many questions to be solved or answered in order to elucidate the optimal treatment or approach.

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