International symposium 8: Newly developed molecular-targeted agents in lung cancer

New ALK inhibitors

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ALK rearrangement was identified to be one of the oncogenic drivers in lung cancer by Prof. Mano’s group in 2007. Crizotinib (CRZ), which had been originally developed as a c-MET inhibitor, was shown to harbor potent inhibitory activity against ALK as well as c-MET. In a phase I study, CRZ showed a dramatic response in patients with ALK-rearranged lung cancer (ALK+ LC). Furthermore, phase III studies comparing CRZ with standard chemotherapy demonstrated superiority of CRZ to standard chemotherapy in both 2nd and 1st line settings, and CRZ has therefore become standard-of-care in the treatment of ALK+ LC.

In addition to CRZ, some novel agents have been recently developed as an ALK inhibitor (ALKi) specifically targeting ALK. Among them, alectinib (ALC) and ceritinib (CRT) achieved high response rates of 94% and 55% in CRZ-naïve and CRZ-treated ALK+ LC, respectively, and these results lead to the approval of ALC and CRT by PMDA and FDA, respectively. Clinical and pre-clinical data showed the association of a variety of secondary mutations in the ALK gene with resistance to CRZ. Both ALC and CRT were shown to be able to inhibit mutated forms of ALK as well as wild-type ALK, and these agents are therefore recognized as the 2nd ALKi after the failure of CRZ in the USA. However, it remains unclear which is a better strategy, sequential therapy with CRZ followed by next generation ALKi or the use of next generation ALKi as 1st ALKi therapy. Although two phase III studies are being conducted to compare CRZ with ALC as 1st line ALKi therapy, the issue has yet to be clarified at present.

In this presentation, I will review the clinical and pre-clinical data of ALKi, and discuss what the best use of ALKi is.