Currently, for the treatment of advanced or recurrent ALK-rearranged non-small cell lung cancer, ALK tyrosine kinase inhibitors are key players. Studies have elucidated the mechanisms of resistance to crizotinib. Those are classified into two groups: 1) ALK signaling dependent including ALK gene secondary mutations and ALK gene copy number gain and 2) ALK signaling independent mechanisms.

The second generation ALK-TKIs have been shown to have more potent and selective to inhibit ALK signaling. In clinical trials, Ceritinib and Alectinib showed the prolonged PFS. In Japan, Alectinib has been approved in 2014 for the patients with second line or after setting.

However even in use of second generation ALK-TKI, resistance is ultimately occur but these mechanisms are becoming clear. The bypass signaling pathway activation through EGFR, c-MET or IGF-1R are reported. Most recently, patient-derived cell line model showed that the Src signaling was activated and Src inhibitors were promising target to overcoming resistance.

In this symposium, I would discuss about the secondary mutation within ALK tyrosine kinase domain and ALK-TKIs, TKI selection and best treatment sequences.