Commentary

Efficacy of crizotinib in *ALK* fusion variants

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In 1995, rearrangement of the anaplastic lymphoma kinase (*ALK*) gene was first reported as a fusion gene in anaplastic large cell non-Hodgkin lymphoma, and in 2005 it was again on focus when Soda *et al.* reported that echinoderm microtubule-associated protein-like4 (*EML4*)-*ALK* fusion gene is a powerful oncogene in lung cancer (1,2). EML4-ALK is a fusion of the intracellular scaffold protein EML4 and the kinase protein ALK. The EML4-ALK fusion protein constitutively activates ALK kinase by forming a coiled-coil domain in the EML4 region (2). About 3–5% of non-small cell lung cancer is positive for EML4-ALK (2). Transgenic mice expressing EML4-ALK develop non-small cell lung cancer (3). Several drugs that inhibit the activity of this fusion gene have been recently developed. Crizotinib that was initially developed as a mesenchymal-epithelial transition factor (MET) inhibitor can also inhibit multiple kinases including ALK. In 2008, crizotinib was used as an ALK tyrosine kinase inhibitor (TKI) in a phase I clinical trial in ALK-positive lung cancer patients (4). The study showed a good overall response rate (ORR; 60.8%) and progression-free survival (PFS; 9.7 months) (4). Thereafter, similar ORR and PFS results were reported in a phase II clinical trial, and the US Food and Drug Administration (FDA) approved it in 2011 (5). Crizotinib became available for clinical use in a very short time (4 years) since its initial report, and is currently the first line therapy for ALK-positive lung cancer. However, subsequent studies have shown frequent recurrence and brain metastasis of ALK-positive lung tumors that are resistant to crizotinib therapy (6-8).

There are at least 10 different variants of EML4-ALK (9). All variants have the essential coiled-coil domain in the EML4 N-terminal portion and in the kinase domain of ALK exon 20 that are necessary for transforming activity. Fusion of exon 13 of EML4 with exon 20 of ALK (variant 1: v1), exon 20 of EML4 with exon 20 of ALK (v2), and exon 6 of EML4 with exon 20 of ALK (v3a/b) are some of the common variants (9). An *in vitro* study has reported that v1, v2, v3a and v3b variants have different sensitivity to crizotinib (10).

Yoshida *et al.* reported very interesting results regarding the effect of crizotinib in ALK fusion variants (11). The authors retrospectively investigated the effect of crizotinib on ORR and PFS in 35 patients with different ALK variants among a total of 55 patients treated with crizotinib between January 2007 and December 2014 (11). The most common ALK variant was v1 (19/35; 54%) followed by v2 (5/35; 14%), v3a/b (4/35; 12%), and other variants (7/35; 20%). The ORR was 69% in all patients, 74% in v1 and 63% in other variants. The median PFS was significantly longer in v1 than in other variants (11.0 *vs.* 4.2 months; $P<0.05$). A multivariate analysis identified two independent factors in association with PFS prolongation: ALK v1 (hazard ratio: 0.350; $P<0.05$) and advanced stage (hazard ratio: 4.646; $P<0.05$) (11). These observations suggest that crizotinib is more effective in tumors with ALK v1 than in other variants.

Based on the study of Yoshida *et al.* it appears that the type of ALK variant may influence the efficacy of ALK-TKI. However, this study has some limitations (11). One limitation is the small population and the second limitation is the retrospective nature of the study that includes patients in various stages of treatment before or after crizotinib. In addition, this study failed to provide data to explain the mechanism behind the effect of v1. An *in vitro* study has shown that the v2 variant has a higher sensitivity to crizotinib than v1 or v3 (10). Further, a previous phase I clinical trial found no difference in response rate between

variants (12). Racial differences may also exist but evidence is lacking. Li *et al.* evaluated the frequency of ALK variants in 7,244 non-small cell lung cancer samples from a North American cohort study and found 200 samples (2.7%) positive for EML4-ALK, and among these 109 (54.5%) were v1, 20 (10%) v2, and 68 (34%) v3 (13).

In addition to crizotinib various ALK-TKIs are currently available. Ceritinib, which is indicated in ALK-positive tumors resistant or refractory to crizotinib, was approved by FDA in 2014, and alectinib, developed in Japan, was approved by FDA in 2016 (14). Other TKIs including brigatinib and lorlatinib are currently awaiting approval for clinical use. The sequential order in which these drugs are used is a controversial issue. Based on a retrospective study Ito *et al.* reported that alectinib is more effective when it is used after crizotinib (15).

Different therapeutic response to epidermal growth factor receptor (EGFR) TKIs depending on the site of EGFR mutation has been previously reported (16,17). Therefore, the effect of ALK-TKIs may similarly differ according to the EML4-ALK variant, and in this connection, the work reported by Yoshida *et al.* is important because it draws attention to this possibility (11). However, a further prospective study in a larger population that includes subjects with different ethnic background would be necessary to confirm these observations.

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Footnote

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