The ALK fusion gene, NPM-ALK, was originally identified in a case of anaplastic large cell lymphoma in 1994, and the EML4-ALK fusion gene was discovered in non-small cell lung cancer (NSCLC) by Drs Soda and Mano in 2007.1 2 This was the first report of identification of a fusion gene in NSCLC. The incidence, according to this first report, of EML4-ALK fusion gene in NSCLC is 6.7%.3 EML4-ALK encodes a transforming fusion kinase, which is a promising therapeutic target for ALK fusion gene-positive (hereinafter ALK-positive) NSCLC. Several fusion partners for ALK other than EML4, such as KIF5B, TFG and KCL1, have also been reported in NSCLC.4 ALK fusion genes have also been detected in several solid tumours other than NSCLC, such as renal cell carcinoma, colon cancer, breast cancer, ovarian cancer, pancreas cancer and inflammatory myofibroblastic tumours,3 4 and ALK inhibitors have been shown to be effective for these cancers also harbouring the fusion gene, similar to the case for EML4-ALK-positive NSCLC.4 5

Crizotinib is the first ALK inhibitor that was initially developed as a MET inhibitor and is also known as an ROS inhibitor.6 The phase III PROFILE 1014 trial was conducted to comparatively evaluate the safety and efficacy of crizotinib as a first-line treatment agent for patients with ALK-positive NSCLC.7 Progression-free survival (PFS) was significantly longer in the crizotinib arm than in the conventional chemotherapy arm (median, 10.9 months vs 7.0 months; HR: 0.45; 95% CI 0.35 to 0.60; p<0.001). The objective response rates (ORRs) were 74% and 45% in the two arms, respectively (p<0.001). In the final analysis of the overall survival (OS) with a median follow-up duration of approximately 46 months, the 4-year survival rate was 56.6% (95% CI 48.3% to 64.1%) in the crizotinib arm and 49.1% (95% CI 40.5% to 57.1%) in the conventional chemotherapy arm.8 After cross-over adjustment, there was an improvement in the OS that favoured crizotinib (HR: 0.346; 95% bootstrap CI 0.81 to 0.718). Based on these data, crizotinib has been established as the standard treatment for ALK-positive NSCLC.

Alectinib is a second-generation, potent, highly selective, central nervous system (CNS)-active ALK inhibitor that was developed in Japan.9 J-ALEX was the first randomised phase III trial comparing crizotinib with alectinib that recruited ALK inhibitor-naive Japanese patients with ALK-positive NSCLC.10 In the second interim analysis, an independent data monitoring committee determined that the primary endpoint (PFS assessed by an independent review facility) of the study had been met (HR: 0.34; 99.7% CI 0.17 to 0.71, stratified log-rank p<0.0001), and recommended an immediate release of the data. The median PFS had not yet been reached in the alectinib arm (95% CI 20.3 to not estimated) and was 10.2 months (8.2–12.0) in the crizotinib arm. Grade 3 or 4 adverse events occurred at a greater frequency in the crizotinib arm (52%) than in the alectinib arm (26%). ALEX, a global phase III trial in which crizotinib was compared with alectinib in patients with ALK-positive NSCLC confirmed the results of J-ALEX, although different doses of alectinib were used in the two trials: 300 mg twice daily in J-ALEX and 600 mg twice daily in ALEX.11 The investigator-assessed PFS was significantly higher in the alectinib arm than in the crizotinib arm; the 12-month event-free survival rates were as follows (alectinib arm vs crizotinib arm): 68.4% (95% CI 61.0 to 75.9) vs 48.7% (95% CI 40.4 to 56.9) (HR 0.47; 95% CI 0.34 to 0.65; p<0.001). Grades 3–5 adverse events were less frequent in the alectinib arm as compared with the crizotinib arm (41% vs 50%). These data indicate that alectinib is more effective and less toxic than crizotinib. Thus, alectinib is highly recommended as a first-line treatment for ALK fusion-positive NSCLC.

Ou et al12 reported patient-reported outcomes (PRO) and health-related quality of life (HRQoL) in a North American phase
II study of alectinib conducted in patients with ALK fusion-positive NSCLC previously treated with crizotinib. Among the 67 patients, the reported ORR was 52.2% and the median PFS was 8.1 months. The PROs and HRQoL benefits were assessed using two self-administered questionnaires, that is, the EORTC QLQ-C30 and QLQ-LC13, at enrolment and every 6 weeks until week 66, disease progression or death. A clinically meaningful improvement of the mean scores was observed in 10 domains, namely the global health status (GHS), social functioning, role functioning, fatigue, pain, dyspnoea, appetite loss, cough, pain in the chest and pain in other parts. A clinically meaningful improvement in the GHS was observed from the first assessment (6 weeks) to week 60. Alectinib appeared to exert a rapid effect, with a median time to symptom deterioration of 1.4 months, based on the composite endpoint of cough, dyspnoea and chest pain, although with prior use of crizotinib. Patients with CNS metastases at baseline experienced comparable HRQoL throughout the duration of the study with patients without CNS metastases. Ou et al. concluded that clinically meaningful improvements in the HRQoL and symptoms were achieved in patients treated with alectinib in this phase II study.

Several other second-generation or third-generation ALK inhibitors such as ceritinib, brigatinib and lorlatinib are also available for clinical use. These agents have been shown to be effective in patients with ALK-positive NSCLC previously treated with crizotinib or alectinib. No clinical data of direct comparisons among these ALK inhibitors are available. However, the toxicity profiles of these agents are different, with gastrointestinal toxicity being the predominant for ceritinib, pulmonary toxicity being the predominant for brigatinib and CNS toxicity being the predominant for lorlatinib. The PRO and HRQoL should be included at least as secondary endpoints. For example, the ARCHER 1050 is a randomised, open-label, phase III study of dacomitinib versus gefitinib in treatment-naive patients with advanced NSCLC. The PFS and OS were significantly longer in the dacomitinib arm than in the gefitinib arm; the median PFS according to a masked independent review was 14.7 months in the dacomitinib arm vs 9.2 months in the gefitinib arm (HR: 0.59; 95% CI 0.47 to 0.74; p<0.0001), and the median OS was 34.1 months in the dacomitinib arm vs 26.8 months in the gefitinib arm (estimated HR: 0.760; 95% CI 0.582 to 0.993; two-sided p=0.044). However, a statistically significant difference in the global quality of life was observed between the two treatment groups, favouring gefitinib (0.20 in the dacomitinib arm vs 4.94 in the gefitinib arm; p=0.0002). Thus, the PRO and HRQoL, especially the global quality of life, should be used as a very important endpoint, in addition to the PFS and OS, in order to evaluate the clinical usefulness of ALK inhibitors.

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