Potential of combination therapy in EGFR mutated lung cancer

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Adderley reviewed studies of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) plus anti-angiogenesis inhibitors for EGFR-mutated lung cancer and focused on the importance of overall survival (OS) data from the NEJ026 study (1). Horinouchi, in his review, outlined the position of using a combination of EGFR-TKI and chemotherapy in standard treatment for EGFR-mutated tumors (2).

A combination of EGFR-TKI plus an anti-angiogenesis inhibitor is promising treatment for patients with EGFR-mutated tumors. Recently, another phase III study, the RELAY study that involved a combination of erlotinib and ramucirumab, showed longer progression-free survival [PFS; 19.4 vs. 12.4 months, hazards ratio (HR) 0.591; 95% confidence interval (CI): 0.461–0.760; P<0.001] (3). Because an effect was not observed after the addition of bevacizumab for a subgroup with brain metastasis in the NEJ026 study, it is thought that the PFS of the RELAY study, excluding brain metastasis, was comparable to the PFS result from our NEJ026 study (16.9 vs. 13.3 months, HR 0.605, 95% CI: 0.417–0.878; P=0.016) (4). A combination of EGFR-TKI plus an anti-angiogenesis inhibitor yielded consistently longer PFS in these two studies, and also in a JO25567 phase II study (16.0 vs. 9.7 months, HR 0.54, 95% CI: 0.36–0.79; P=0.0015) (5). The three studies also demonstrated an effect on tumors with an L858R subtype, which respond poorly to EGFR-TKI monotherapy compared to tumors with an exon 19 deletion.

Osimertinib monotherapy has been approved as first-line treatment for lung cancer with an EGFR mutation in Japan. The first priority of first-line treatment for this disease became osimertinib monotherapy. Recently, updated OS data for an Asian subgroup in the FLAURA study was reported in ESMO. In the Asian subgroup, osimertinib did not yield an OS benefit and the Kaplan-Meier curve for OS was crossed at 40 months (HR 0.995, 95% CI: 0.752–1.319). This data encourages the development of combination treatment due to achieving longer OS as a substitute for first-line osimertinib treatment. In a L858R mutation subgroup, osimertinib was not superior to first generation EGFR-TKI (HR 0.996, 95% CI: 0.708–1.404). A combination of erlotinib and an anti-angiogenic inhibitor, equally active for the L858R mutation as well as the exon 19 deletion, is considered a promising candidate for the treatment of tumors with an L858R mutation. When osimertinib use as a second or more line of TKI treatment, osimertinib is usable just after the detection of a T790M mutation in Japan. In this situation, we need to understand whether T790M-resistant mutations occur with the same frequency in combination treatment with EGFR-TKI and an...
anti-angiogenesis inhibitor as in EGFR-TKI monotherapy. Although the BELIEF study described how a combination of erlotinib plus bevacizumab showed more efficacy in de novo T790M tumors compared to T790M negative tumors (6), both NEJ026 and RELAY studies showed the same frequency of T790M mutations after the failure of combination treatments compared to erlotinib monotherapy. This result implied that sequential osimertinib treatment may achieve longer OS by the prolongation of EGFR-TKI treatment after the emergence of T790M mutations.

We have now collected and are currently analyzing OS data from NEJ026. We hope to be able to present this information at major international conferences this year.

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Footnote

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