NEJ026 trial: progression-free survival benefit is not enough

Author's reply

Fei Liang expressed an important concern regarding lack of overall survival events (ie, deaths) for assessment of overall survival in the NEJ026 study[1] and in the combined analysis of NEJ026 and the JO25567 study.[2] We agree that overall survival is the most crucial factor to consider when evaluating benefits of drugs for patients with cancer. If overall survival had been selected as the primary endpoint in NEJ026, we would have required approximately 500 to 1000 patients. However, we selected progression-free survival as the primary endpoint and explain our reasons below.

First, Liang calculated the sample size based on the overall survival data from JO25567 presented at the American Society of Clinical Oncology conference (Chicago, IL, USA) in 2018 (hazard ratio 0·81, 95% CI 0·53–1·23). When we were drafting the NEJ026 protocol, the full progression-free survival data of the JO25567 study was known but the comparison overall survival data was not shown due to immaturity. Therefore, we had no appropriate data to calculate sample size for overall survival at that point.

Second, although we are planning to re-evaluate survival events at the end of 2019, the data might still be immature. Most Japanese studies on patients with non-small-cell lung cancer (NSCLC) have achieved longer overall survival than studies done in the UK, Europe, the USA, and Canada. This longer overall survival is hypothesised to be because of easier access to anticancer treatment and racial differences. In the LUX-Lung3 study,[3] overall survival of Japanese patients was more than 45 months. When patients attain long overall survival after second-line or higher treatment, the influence of the first-line treatment on overall survival decreases.[4] Moreover, the third-generation EGFR tyrosine-kinase inhibitor osimertinib was approved for T790M-positive NSCLC refractory to second-line or higher treatment. Longer survival of patients given osimertinib will be expected. Validation of overall survival data for patients who are *EGFR*-positive would take nearly a decade and risks the experimental group becoming out of date. Consequently, in studies using progression-free survival as the primary endpoint, the efficacy of the drug should be judged by progression-free survival data, and overall survival data should be assessed not by significance but by degree of concordance with progression-free survival. Evaluation of time to second objective disease progression (PFS2) has been included in the NEJ026 study to complement immature overall survival data. Although PFS2 has not yet been validated as a surrogate marker for overall survival, these data will be collected until the end of 2019, before matured surival data. However, the combined analysis of JO25567 and NEJ026 will be done several years after we have completed the overall survival and progression-free survival analyses, for which we have given the end of 2019 as a cutoff date.

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