NEJ026 trial: progression-free survival benefit is not enough

In *The Lancet Oncology,* Haruhiro Saito and colleagues report the NEJ026 trial,[1] in which bevacizumab plus erlotinib combination therapy significantly improved progression-free survival (hazard ratio [HR] 0·605, 95% CI 0·417–0·877) compared with erlotinib alone in patients with *EGFR*-positive non-small-cell lung cancer (NSCLC), which is consistent with the results of progression-free survival in the phase 2 JO25567 study (HR 0·54, 95% CI 0·36–0·79).[2] As Saito and colleagues claimed, they designed the NEJ026 trial because results of the phase 2 JO25567 study cannot be deemed entirely conclusive because the study was inadequately powered to assess overall survival. However, in the NEJ026 study, the authors used progression-free survival rather than overall survival as the primary endpoint. In the JO25567 trial, the combination therapy is associated with a non-significant of overall survival benefit (HR 0·81, 95% CI 0·53–1·23). To validate the reported overall survival results, 707 overall survival events (ie, deaths) were required to detect a HR of 0·81 with a significance level of 5% and a detection power of 80%. The authors prespecified a combined analysis of overall survival data from NEJ026 and JO25567, but only 382 participants were enrolled in the two trials. Hence, even in the ideal situation in which all participants were followed-up until death and none lost to follow-up, the pooled analysis could not accumulate the number of deaths needed to reach a confirmatory conclusion. Furthermore, the magnitude of benefit in progression-free survival observed in NEJ026 is numerically smaller than that in JO25567, suggesting that the magnitude of potential overall survival benefit might also be smaller, which would need even more deaths. Without an overall survival benefit, progression-free survival is an inadequate measure of net clinical benefit in assessing the efficacy of combination therapy when the two drugs have independent anticancer activity,[3] such as how erlotinib monotherapy[4] and bevacizumab in combination with first-line platinum-based chemotherapy[5] have been proven to provide efficacy for non-squamous NSCLC. Moreover, the use of both drugs in first-line therapy precludes the option of reserving one drug for the treatment of disease progression and increases toxicity and cost compared with a single drug.

In conclusion, the reported progression-free survival benefit is inadequate to establish the role of erlotinib plus bevacizumab combination therapy as the standard first-line therapy for patients with *EGFR*-positive NSCLC and Saito and colleagues should report the statistical consideration for overall survival analysis, including the assumption of expected treatment effect and number of events needed.

I declare no competing interests.

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