

In Reply Regarding the 2-stage test design, we applied in the CCTG HN.6 study the following stepwise test procedure (Figure 1 by Wang et al), which controls the overall type I error rate at 5% used to analyze progression-free survival (PFS):

1. In the first step, whether accelerated-fractionation radiotherapy (AFX) plus panitumumab is superior to standard-fractionation radiotherapy (SFX) plus cisplatin is tested using a stratified log-rank test.
2. If the 2-sided P value of the stratified log-rank test is greater than 0.05 (ie, superiority of AFX plus panitumumab to SFX plus cisplatin is not demonstrated), a test for the noninferiority of AFX plus panitumumab to SFX plus cisplatin is performed that also includes all randomized patients. Noninferiority of AFX plus panitumumab to SFX plus cisplatin is claimed when the upper limit of a 2-sided 95% confidence interval for the hazard ratio of AFX plus panitumumab to SFX plus cisplatin, derived from a stratified Cox model adjusting stratification factors at randomization with a single treatment covariate, is less than or equal to 1.15.

Regarding power for the noninferiority test, we agree with Cheng et al that a large number of events (ie, 1650) is needed to have 80% power for noninferiority when 2 arms have the same distribution. However, as stated in the study protocol, when the study was designed, we expected a certain amount of efficacy for the experimental arm (AFX plus panitumumab); therefore, with 246 events observed at the time of final analysis for this study, we would have 80% power to claim noninferiority at a 5% level if the true hazard ratio of AFX plus panitumumab to SFX plus cisplatin was not higher than 0.81 (which corresponds to a difference not lower than 7.6% in the 2-year PFS between the AFX plus panitumumab arm and the SFX plus cisplatin arm).

Regarding that the study was underpowered for both the superiority test and noninferiority test, this limitation has already been discussed in our article.

We thank Cheng et al for pointing out the potential use of restricted mean PFS time as an alternative way to test noninferiority. We have calculated the 36-month restricted mean PFS time for AFX plus panitumumab and SFX plus cisplatin as 29.31 and 28.46 months, respectively. The upper bound for the confidence interval for the difference of the 36-month RMST for SFX plus cisplatin vs AFX plus panitumumab was 1.82 months, which is close to the 1.7 months estimated by Cheng et al based on data scanned from Figure 2 of our article, but greater than 5% of 36 months. We will consider the design of clinical trials with this methodology in the future.

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Conflict of Interest Disclosures: None reported.
