Binning of Exposures in Survival Analysis for Oncology - A Simulation Study

Matts Kågedal1*, Shang-Chiung Chen1, Russ wada2, Jin Y Jin1

1Genentech Inc, San Francisco, CA; 2Quantitative Solutions, Menlo Park, CA

Objectives: To evaluate the impact of binning patients based on exposure by quartiles, tertiles or twotiles on the ability to 1) detect an E-R trend; and 2) compare efficacy in the low exposure treatment bin over control.

Methods: A simulation study was performed assuming a 2-arm oncology trial with n=100 per arm. Two E-R scenarios were assumed; 1) No E-R trend and a hazard ratio (HR) of 0.67 across all exposure levels. 2) Marked E-R trend where the HR ranged from 1 to 0.4 from low to high exposure. The simulated trials were evaluated using Cox regression after binning exposure by quartiles, tertiles and twotiles. The assessment was based on an 80% CI (CI80) and the point estimate (HRPE).

Results: In scenario 1 (no E-R trend), the likelihood of correctly identifying a benefit of treatment (CI80<1) at low exposure based on quartiles was 61%. This was worse than tertiles and twotiles which had a likelihood of 70% and 79% respectively. With quartiles there were more spurious results based on the HRPE with 18% of the simulations suggesting an ER-trend (HR of high bin lower than the low bin by at least 0.2). When analyzing scenario 2 (no benefit in the lowest quartile and a marked ER relation), the likelihood of showing similarity to control in lowest exposure bin was 0% based on CI80 and 63% based on the point estimate (HRPE=0.8-1.25), clearly lower compared to tertiles and twotiles. The likelihood of detecting an ER-trend was highest based on quartiles at 91% based on CI80 which was slightly better than tertiles at 89% and clearly better than twotiles at 85%.

Conclusions: The proposed clinical trials simulations approach enabled a quantitative evaluation of a key component of the E-R analysis plan. Binning by tertiles appears to provide the best ability to draw correct exposure-response conclusions in the tested oncology trial design.