Democratizing Bayesian joint models in clinical drug development: From premise to daily practice in oncology

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Abstract

It takes time for new technology to be appreciated, tested, and used by the broader statistical community in the pharmaceutical industry. In this presentation, we share lessons learned in raising Bayesian joint models from intuition to being part of the standard tools supporting decisions in oncology clinical development at Roche-Genentech. The development is articulated in 5 parts reflecting the history of the project: (1) formulating the clinical question, (2) defining the estimand, (3) building confidence in the joint model estimator and comparing it with traditional approaches, (4) communicating the results to a clinical audience, and (5) developing an open-source R package jmpost to enable the regular application of joint models across multiple projects and facilitate communication with stakeholders. Our motivation is to estimate the effect of treatment on tumor burden in trial participants with solid tumors and its consequences on overall survival (OS). Changes in tumor size are adequately described by

bi-exponential mixed effects models, and parametric (e.g. Weibull) survival models are proposed to describe OS. Various options can be considered to relate tumor size to OS. In our experience, the predicted value (or slope) for tumor size at time t is not the best link. The death hazard does not seem to be driven by sudden changes in tumor burden. Instead, measures summarizing changes in tumor size in the medium term, like the tumor re-growth rate, give better predictive performance and capture a pharmacologically sensible process. Also, it offers a computationally efficient alternative to time-dependent links. Specific challenges faced on this project are discussed, which include: priors' elicitation, choice of best link function, comparison of various solutions for random effects integration, and assessment of goodness-of-fit.