Surv-CRM-12: A Bayesian phase I/II survival CRM for right-censored toxicity endpoints with competing disease progression

Anaïs Andrillon[1,2], Sylvie Chevret[2], Shing M. Lee[3], Lucie Biard[2]

[1] *Department of Statistical Methodology, SARYGA, Tournus, France*
[2]*INSERM U1153 Team ECSTRRA, Université Paris Cité, Paris, France*
[3]*Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, USA*

Abstract

The growing interest in new classes of anti-cancer agents, such as molecularly targeted therapies (MTAs) and immunotherapies, has changed the dose-finding paradigm. In this setting, the observation of late-onset toxicity endpoints could likely be precluded by trial discontinuation due to disease progression, defining a competing event to toxicity. We aimed to provide a phase I/II dose-finding design that allows the dose-limiting toxicity (DLT) outcomes to be delayed or unobserved due to competing progression within the possibly long observation window. In this competing risks framework, we propose a design for phase I/II trials targeting the subdistribution hazard function of toxicity and progression for dose-finding, with model parameters estimated using Bayesian inference. The proposed design named the Survival-Continual Reassessment Method-12 (Surv-CRM-12), aimed at identifying a dose that optimized the progression outcome among a set of acceptable doses. In a simulation study, design operating characteristics were evaluated and compared to the TITE-BOIN-ET design and a nonparametric benchmark approach. The performances of the proposed method were consistent with the complexity of scenarios as assessed by the nonparametric benchmark. We found that the proposed design presents desirable operating characteristics in selecting the optimal dose and safety.