Statistical Significance Piece

Clinical trials of new anticancer therapies are critically important in the search for more effective cancer treatments. The major objective in phase I trials is to identify a working dose for subsequent studies. Phase I trials represent the first testing of an investigational agent in humans and act as a point of translation of years of laboratory research into the clinic.

The widely used standard 3+3 design has much less rigorous statistical basis than model-based designs described in the more recent literature, such as the continual reassessment method (CRM) and the method of escalation with overdose control (EWOC). Both types of designs, however, are subject to stop and go in patient accrual due to staggered patient entry to the trial, and as such discourage enrollment and can result in prolonged trial duration. In addition, data of patients with early drop-out not due to safety reasons are excluded from analysis and decision making.

An oncology phase I dose-finding study is presented and discussed, where the standard of care is combined with a novel regimen. After evaluating the biologic mechanism and data generated from toxicology studies, the dose limiting toxicity (DLT) observation window was set as 9 weeks to estimate the Maximum Tolerated Dose (MTD). To address the issues with long observation time and patient drop-out, we employ the time-to-event continual reassessment method (TITE-CRM), initially proposed by Cheung and Chappell (2000), a Bayesian dose-finding design incorporating information not only from patients observed for the entire observation period but also from patients observed for less than the full observation period. TITE-CRM uses a weighted binomial likelihood with weights assigned to observations by the unknown time to toxicity distribution, and is open to accrual continually. To avoid dosing at overly toxic levels while retaining accuracy and efficiency, we propose an alternative adaptive weight function by incorporating cyclical data with parameters updated continually. This provides a reasonable estimate for the time to toxicity distribution by accounting for inter-cycle variability and maintains the statistical property of consistency and coherence.

Design calibrations for the clinical and statistical parameters are conducted to ensure good operating characteristics. Simulation results show the proposed TITE-CRM designs with adaptive weight function are significantly shorter, maintain advantages of the CRM relative to the 3+3 design, and do not expose patients to significant additional risk. The trial is currently ongoing, and it’s projected that the duration of the study will be shortened by 1-1.5 years.