A Bayesian latent-subgroup phase I/II platform design to co-optimize doses in multiple indications

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Abstract

The US Food and Drug Administration (FDA) launched Project Optimus to reform the dose optimization and dose selection paradigm in oncology drug development, calling for the paradigm shift from finding the maximum tolerated dose to the identification of optimal biological dose (OBD). Motivated by a real-world drug development program, we propose a master-protocol-based platform trial design to simultaneously identify OBDs of a new drug, combined with standards of care or other novel agents, in multiple indications. We propose a Bayesian latent subgroup model to accommodate the treatment heterogeneity across indications, and employ Bayesian hierarchical models to borrow information within subgroups. At each interim, we update the subgroup membership and dose-toxicity and -efficacy estimates, as well as the estimate of the utility for risk-benefit tradeoff, based on the observed data across treatment arms to inform the arm-specific decision of dose escalation and de-escalation and identify the optimal biological dose for each arm of a combination partner and an indication. The simulation study shows that the proposed design has desirable operating characteristics, providing a highly flexible and efficient way for dose optimization. The design has great potential to shorten the drug development timeline, save costs by reducing overlapping infrastructure, and speed up regulatory approval.

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