Phase I Dose-Escalation Designs in Oncology using time to event methods Statistical Properties and Applicability

Project background & overview:

Non cytotoxic therapies such as molecularly targeted therapies and immunotherapies are often associated with toxicities occurring after the first cycle of treatment. Broader DLT definitions with longer pre-defined DLT/safety observation periods may therefore be relevant to consider.

Standard dose-finding designs, typically focused on acute toxicities occurring through the end of cycle1, can rapidly characterize the maximum tolerated dose, but require later dose reduction or MTD reassessment in case of late onset DLTs.

A distinction between cycle 1 acute toxicity, prolonged toxicity impacting on tolerability and late severe toxicity may be informative. Even when dose escalation decisions are based on the first cycle, the estimation of the MTD can incorporate toxicities across a predefined number of cycles in a longitudinal or time-to-event approach. The use of adaptive designs or methods such as the time-to-event model assisted or based designs, which consider toxicities arising beyond the first cycle of treatment, could provide a better estimate of the MTD for long-term treatment.

The goal of this project is to develop Bayesian statistical approaches with the aim to optimize the dose-finding in case of early and late toxicities, to assess the statistical properties of time to event designs and analyse the challenges in their application

The trainee will

- Implement a number of early phase oncology dose finding designs based on time to event approach
- Develop any relevant extensions/modifications of the established time to event designs
- Evaluate the designs' performance in a comprehensive simulation study
- Get in-depth knowledge of the practical aspects of dose finding

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About the role:

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References:

Ying Yuan et al: Time-to-Event Bayesian Optimal Interval Design to Accelerate Phase I Trials

Erik van Werkhoven et al: Practicalities in running early-phase trials using the time-to-event continual reassessment method (TiTE-CRM) for interventions with long toxicity periods using two radiotherapy oncology trials as examples

Meizi Liu et al: PoD-BIN: A Probability of Decision Bayesian Interval Design for Time-to-Event Dose-Finding Trials with Multiple Toxicity Grades

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