Proposition de stage

Titre

Evaluation of time to event dose-escalation designs in early phase oncology trials

Sujet

Phase I clinical trials are the first stage of human experimentation of a new treatment and mainly aim at evaluating the safety of various doses of the drug in a small number of subjects. In oncology, the standard assumption made is that both the probabilities of toxicity and efficacy should increase with the dose. The main objective of phase I trials in oncology is therefore to determine a dose with an acceptable probability of toxicity, known as the maximum tolerated dose (MTD), which may exhibit a higher chance of anti-tumor activity in future trials than a lower dose.

Due to ethical constraints, sequential dose-escalation designs have been proposed to determine the MTD. In these designs, patients are included by cohorts of small sample size and the dosing decision is made based on all accumulated toxicity data after each cohort has been followed up for a predefined duration. However, for anti-cancer agents causing late onset toxicities, the toxicity follow-up period may need to be extended. In this case, waiting for all patients to be completely followed up would lead to a too long study duration.

To reduce the trial duration in this context while maintaining accuracy and safety, Bayesian time to event (TITE) designs have been developed where the dosing decisions can be made from partial follow-up information.

The objective of this internship is to study various TITE designs (mainly model-assisted or model-based) and evaluate their performance using simulations under various settings (as the impact of the rate of accrual, cohort size, time of toxicity etc.). The second objective is to participate in the user-friendly implementation of these approaches to facilitate their use in clinical trials.

Profil

Niveau BAC+5 en statistiques, informatique, ou mathématiques appliqués (grandes écoles d'ingénieur type ENSAI, ISUP, INSA, Master 2 Université, …)
Excellente maîtrise de R indispensable.
Excellente compréhension des concepts de base des statistiques bayésiennes.
Rigueur scientifique, autonomie, bon relationnel, bon niveau d'anglais.

Mission

Durée : 6 mois
Début : Entre février et avril 2023
Lieu : Chilly-Mazarin (91)
Rémunération : 7.80€ brut par heure

Tuteur

Emma GERARD – Biostatistics & Programming – Statistical Innovation Hub:
emma.gerard@sanofi.com

References

- Chevret, S. Statistical Methods for dose-Finding Experiments. Statistics in Practice. John Wiley and Sons Ltd., Chichester, 2006.
- Cheung, Y. K., & Chappell, R. (2000). Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics, 56(4), 1177-1182.
- Bekele, B. N., Ji, Y., Shen, Y., & Thall, P. F. (2008). Monitoring late-onset toxicities in phase I trials using predicted risks. Biostatistics, 9(3), 442-457.
- Yuan, Y., Lin, R., Li, D., Nie, L., & Warren, K. E. (2018). Time-to-Event Bayesian Optimal Interval Design to Accelerate Phase I Trials. Clinical Cancer Research, 24(20), 4921-4930.
- Lin, R., & Yuan, Y. (2020). Time-to-event model-assisted designs for dose-finding trials with delayed toxicity. Biostatistics, 21(4), 807-824.