ESR Researcher Project: Non-technical Summary

"Innovative designs for combination of therapies"

Team: Jose Luis Jimenez, Roberto Fontana

The use of drug combinations in clinical trials has emerged during the last years as an alternative to single agent trials since a more favorable therapeutic response may be obtained by combining drugs that, for instance, target multiple pathways or inhibit resistance mechanisms. This practice is common in both early phase and late phase clinical trials. However, depending on the phase of the trial, we may find different challenges that will require novel methodology. In early phase, where we model the probability of toxicity and efficacy, the main challenge is to find a suitable multivariate model that works well with a relatively low sample size. In late phase trials, the main challenge is to propose a design that allows to perfectly control the type-I error and the power while allowing for the trial to stop in case of a lack of efficacy or in case the interim analyses show an efficacy that is big enough so it would be unethical to continue the trial. Other challenges may involve certain characteristics of the drug, such us delayed effects. This issue is quite present nowadays in clinical research because of the use of immuno-therapy against cancer.

In early phase trials, we studied the state of the art methodology and we observed that a large number of published methods are not appropriate for drug combination settings since were originally designed for single agents and then adapted to drug combinations. This statement is not based only performance, because in fact many of these methods perform quite well even though they were not designed to be used in a drug combination setting, but because most of them do not take into account the interaction between drugs.

In late phase trials we focused our attention in the design of clinical trials in the presence of delayed effects in a drug combination setting. We performed a state of the art methodology review, and we observed that there is enough published methodology to design efficient confirmatory trials under this conditions. However, we also observed that most of this methodology primarily focuses on power recovery rather than type-I error rate control, which makes it difficult to apply in practice given the nature of confirmatory trials.

Our intention during this thesis was not only to develop novel methodology but to do it in areas that could be of interest for clinicians. In this thesis we make three contributions to the field of clinical trials with drug combinations. In early phase trials, we propose a Bayesian adaptive phase I trial design that allows the investigator to attribute a DLT to one or both agents in a unknown fraction of patients, even when the drugs are given concurrently. We also propose a Bayesian adaptive phase I/II design with drug combinations, a binary endpoint in stage 1, and a TTP endpoint in stage 2, where we aim to identify the dose combination region associated with the highest median TTP among doses along the MTD curve. In late phase trials, we did an assessment of the impact of delayed effects in group sequential and adaptive group sequential designs, with an empirical evaluation in terms of power and type-I error rate of the weighted log-rank in a simulated scenario.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.

Our last contribution includes several practical recommendations regarding which methodology should be used in the presence of delayed effects depending on certain characteristics of the trial.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.