ESR Researcher Project: Non-technical Summary

"Investigation of the gain in efficiency from using a Gamma threshold model for joint modelling of PFS and OS in oncology trials"

Team: Enya Weber, Andrew Titman

In oncology trials, different clinical endpoints can be considered for the analysis of overall survival (OS). Time-to-progression (TTP) is defined as the time from study entry to recurrence of the disease (e.g. tumour growth). Progression-free survival (PFS) represents the time from study entry until cancer progression or death depending on what occurs first.

OS is the most important endpoint but often TTP or PFS are strongly related to overall survival. Observing OS may require long follow-up after time-to progression, long and expensive trials might be the consequence. Progression-related endpoints are often used for the evaluation of treatment effects on OS in order to gain efficiency in terms of costs and time. PFS can also be used as a direct surrogate endpoint for OS for some cancers but is too stringent as an assumption for other type of cancers. Existing challenges of assessing the efficiency in the analysis of OS using information on progression are to adequately model the joint distribution of PFS and OS. It is of interest to investigate the extent to which existing modelling approaches can increase the efficiency in assessment of the treatment effects on survival using PFS.

One framework for modelling PFS and OS is based on assuming a semi-competing risks model, where a patient can experience both a terminal event and nonterminal event. The terminal event such as death censors the nonterminal event such as progression but not vice versa. A new approach [1] of modelling semi-competing risks data considers the events to arise through the first passage times of an unobserved stochastic growth process. In other words, it can be considered as a threshold model with a fixed level for death and a level for progression of cancer. If the time crosses the level for relapse first, the random growth continues until the level for death has been crossed. If the process crosses the level for death first, it is stopped.

Our initial work in this project was to analyze this modelling approach in terms of the implied transition hazards between the states of the observable process. So far, we have derived an expression for the overall survival hazard function, the hazard function given progression and the hazard function without progression based on this new modelling approach. In addition, we have extended the modelling approach to include covariates such as treatment.

We are currently investigating the performance of the modelling approach by conducting simulations. Our aim is to investigate the extent to which the extended modelling approach can increase efficiency in estimating the treatment effect on OS. One way to do that is to

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.

compare the extended approach with a simplified approach. In this modified approach, only death is modelled and the information on progression is ignored, therefore only parameters relating to OS need to be estimated.

We will then apply both models to the same data and compare the hazard functions for OS for the two models and investigate if the extended approach including progression works better in terms of estimation of overall survival and standard error, and for which scenarios. We also plan to illustrate the extended approach by using data from a clinical trial of treatments for colon cancer.

Reference:

[1] Sildnes, B. , Lindqvist, B. H. (2017). Modeling of semi-competing risks by means of first passage times of a stochastic process. Lifetime Data Analysis, 1-32

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.