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A Design for Phase II Clinical Trial with Efficacy and Toxicity Outcomes and Prognostic Variables

Background

PePs2 is a phase II clinical trial of Pembrolizumab in non-small cell lung cancer patients. The primary objective of the trial is to learn if the treatment is associated with sufficient efficacy and an acceptably low level of toxicity to be given to performance status 2 patients. Patient-specific factors will likely affect whether patients achieve a good response. Two prognostic variables of note are: (a) the expression level of the PD-L1 protein; and (b) whether the patient has been treated before.

Challenge

Existing phase II trial methodologies allow the simultaneous scrutiny of efficacy and toxicity but do not generally admit explanatory (or prognostic) variables. Could we come up with a trial design that uses the prognostic data to selectively approve the treatment only in the patient subgroups where it is shown to work?

Results

We developed a novel Bayesian trial methodology called BeBoP that studies correlated binary efficacy and toxicity outcomes. Importantly, BeBoP admits continuous and binary explanatory variables so we could control for the fact that patients have different expression levels of the PD-L1 protein. Using a broad simulation study, we demonstrated that BeBoP performs well across a wide range of scenarios. In PePs2, BeBoP let us avoid the unappealing prospect of running separate trials for good and poor prognosis patients.

Computational Complexity

The Bayesian statistical method fuses prior beliefs with observed data and generally involves calculus. There are five-parameters in BeBoP so the update integral is five-dimensional. Such integrals can be solved using numerical methods like Monte Carlo integration or cubature but it is a costly computational exercise. In our simulation study, each trial calculated eight of these integrals. We studied 16 scenarios and performed 10,000 replicates in each scenario, meaning that 1.28m integrals had to be calculated. If each took 1s, this would require roughly 15 days of processing time. We were able to complete the simulations in less than a day thanks to the massive opportunity for parallel processing in BEAR.

Case study

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GitHub: https://github.com/brockk/clintrials/tree/dev

Product Used
Python, NumPy, SciPy and PANDAS

Funding
Cancer Research UK
Bloodwise (formerly LLR)

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Submitted August 2015