Automated Population Power Analysis Using The S-ADAPT MC-PEM Scripting Program: Application to Oncology Biotherapeutics

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ABSTRACT

Objective: The combination of Population-fitting and simulation procedures is necessary to estimate the probability of obtaining successful outcomes in future trials (Power). The success of these procedures depends on the generation of a large number of data sets that are run through the same cycle of simulation/fitting which ultimately allows one to design the optimal trial with the required power. The S-ADAPT program offers easy ways to automate all these steps with minimum of scripting language. At the same time, the optimization techniques necessary to estimate the model parameters from each simulated data set combine both advanced deterministic and stochastic algorithms that make the program robust, efficient and usable for even very complex models. These optimization methods include direct sampling, iterative two-stage, importance sampling expectation maximization (IMM), importance sampling EM facilitated by determinantal techniques to increase convergence efficiency. The S-ADAPT program most suitable for large scale fitting procedure often required for the design of new studies.

RESULTS

In this exemplary study we characterized the dose (PK) response (Tumor Volume) relationship with minimal in vivo experimentation. A multiple dose in vivo study was performed on both hematopoietic (BM) and our primary antibody candidate antibody. The biological processes (tumor growth, binding of drug to target) and Pharmacokinetics of the drugs were translated into a mathematical framework using the data from the study.


MODEL DEVELOPMENT

In this study, we have developed the S-ADAPT MC-PEM Scripting.

MODEL DIAGRAM

- **Experimental Growth**
- **Drug in Blood**
- **Target Mediated Clearance**

- **Drug concentration**
- **Drug concentrations**
- **Duration of drug**

- **Tumor Volume**
- **Tumor Volume growth inhibition**
- **Due to drug**

- **Dose**

- **Drug Treatment**

- **Drug**

- **Drug Exposure**

- **Target**

Fitting procedure
- **The S-ADAPT model was fit to the 200 data sets with (potential ability to be different between the two drugs) and without covariate analysis (some potential was estimated in the model)**
- **The goal was to estimate the probability to detect superiority in favor of our drug (statistically significant superiority on in vivo potency of drug in favor of our drug).**
- **We chose to fit the model to estimate the probability of obtaining successful outcomes in future trials (Power) with the required power.**

CONCLUSION

A large number of Population fitting and simulation procedures were performed automatically using the S-ADAPT scripting program and helped designing future studies. The automated system was run for two days without any additional man power intervention. Both the EM algorithms and optimized scripting facility makes the S-ADAPT program most suitable for large scale fitting procedure often required for the design of new studies.

References:

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