

PK/PD Modeling, Biomarkers and Clinical Endpoints: The Use of Cluster Analyses, Logistic Regressions, and Receiver Operator Characteristics (ROC) for Efficient Drug Development

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INTRODUCTION

The escalating costs and low productivity of drug development have been well documented over the past several years. The FDA in its Critical Path initiative and other agencies are calling upon new methods such as PK/PD modeling, biomarkers and clinical endpoints to improve development processes. Advanced statistical methods such as cluster analyses (CA), logistic regressions (LR), and Receiver Operator Characteristics (ROC) may be combined with PK/PD modeling methods to provide additional insights for the analysis of biomarkers and clinical endpoints

METHODS

PK/PD modeling, along with CA, LR, and ROC techniques were used to analyze biomarker data and binary clinical endpoints. Two Case-studies are presented in the Results section to illustrate how these techniques may help answering key questions.

RESULTS

CASE STUDY I : Biomarker, Clinical Outcome and Adaptive Trial

Data:

A Phase II study was conducted in patients with an immune disease (4 treatment groups; 1 placebo and 3 active dosing groups). A total of 16 different biomarkers were collected (Weeks 0, 1, 3, 6, 9, 12, 16, 20 and 24) and the clinical endpoint was assessed on week 24.

Objective:

To evaluate biomarker data over time to maximize the prediction of a clinical response on Week 24 (a binary outcome) in order to develop an adaptive trial.

Results and Discussion:

In a first step, ROC analyses were performed to identify the biomarker that best predicted the clinical outcome. Biomarker No. 12 was identified as the most sensitive one to predict the clinical outcome (area under ROC curve = 0.70).

In a second step, the ROC analysis was extended by including a time component. Overall, results showed that biomarker values at Week 3 further improved the predictive performance of the biomarker.

Finally, a cut off concentration value of Biomarker No. 12 at Week 3 was determined in order to maximize the predictive performance. Concentration of Biomarker No. 12 less than 5 ng/mL were associated to a 32% probability of response while concentration greater than 5 ng/mL were associated to a 65% probability of response. The above biomarker, time, and concentration cutoff were used to design an adaptive trial.

CASE STUDY II : Clinical Response, Sub-Populations and Pivotal Trials

Data:

The following Phase II studies were conducted for a CNS drug:

Study A : Placebo, Dose Level II

Study B : Placebo, Dose Level I, II and III

Study C : Placebo, Dose Level II

Based on Hamilton scores, the above studies resulted in sub-optimal clinical response in the overall population and the systemic exposure of the parent product was saturated at dose levels II and III.

Objective:

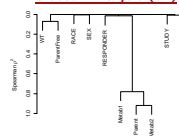
Determine sub-populations that displayed an adequate clinical response to treatment, and the underlying factors responsible for the clinical response (e.g., demographics, drug exposure, baseline Hamilton score ...)

Results and Discussion:

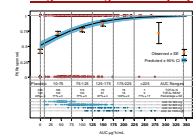
Based on PK modeling, parent drug exposure was saturated whereas metabolites could be increased with higher dose levels. On the other hand, PK/PD analyses showed that metabolites did not contribute to clinical efficacy, preventing one to increase clinical response by increasing the dose. Logistic regression detected that trough concentrations and baseline Hamilton scores were the most significant covariates. Based on a ROC analysis, patients with trough levels above 250 ng/mL and baseline Hamilton scores less than 10 maximized the probability of a clinical response from 25% to 52%. Overall, sub-populations of responders were identified with the above logistic/ROC analysis in order to better design a pivotal trial.

Examples of Visual Outputs

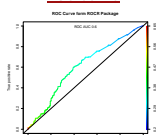
Cluster Analysis (CA)



Logistic Regression (LR)



ROC Curve



ROC Analysis



CONCLUSION

Research groups implementing PK/PD modeling and statistical tools such as CA, LR, and ROC methods should have a competitive advantage. These techniques provided additional insights and guidance for effective drug development and for the design of adaptive/pivotal clinical trials.