Clinical Trial Simulations to Assess the Probability of Revealing Biomarker Dose-Response in Ph1 Trials

Tong Lu1, Yuying Gao2, Lichuan Liu1, Alex Huang1, Amita Joshi1, Jin Yan Jin1*

1Genentech, Inc., South San Francisco, CA; 2Quantitative Solutions, Menlo Park, CA

Objectives: For rational dose selection of targeted anticancer agents, it is critical to obtain early assessment of clinical activity and target modulation. However, in Ph1 dose escalation, biomarker dose-response (D-R) assessment based on tumor biopsy data is challenging, considering the uncertainty around efficacious dose, small sample size, high inter-subject variability, and high biopsy failure rate. The objective of this work is to assess the power of detecting biomarker D-R relationship by clinical trial simulations.

Methods: 1) Simulation: Based on available biomarker D-R relationship (inhibitory Emax model), 3 scenarios were simulated with ED50 within, below, or above Ph1 dose range. For each scenario, 1000 sets of parameters were generated, incorporating uncertainty and inter-trial variability for ED50 (assume 75%), and observed variability for baseline E0 (sampling with replacement). The pre- and post-treatment data were simulated for each subject, with 1000 subjects/dose for 6 dose levels. 2) Bootstrapping: for each scenario, 1000 Ph1 trials (n=9/trial: 3 subjects/dose, 6 dose levels, 50% failure rate regardless of dose) were generated by resampling from simulated subjects; 1000 sets of bootstrapped parameters were derived by fitting to the Emax model. 3) Evaluation criteria: a) power of detecting D-R relationship (ie, ED50) was assessed by % of bootstrapped parameters falling into predefined interval ([0.7-1.3]) of true value; b) success rate of achieving certain target inhibition at certain dose.

Results: In this specific case, when ED50 was in the middle of the dose range, the power of detecting true ED50 was decent (49%) in spite of small sample size and high failure rate; for scenarios where ED50 was below or above the dose range, the powers went down significantly (drop more pronounced when above the range). Simulation also suggested strong likelihood of ED50 underestimation when ED50 was above the dose range.

Conclusions: To inform oncology biomarker strategy, theoretical simulations can be conducted with varying assumptions to assess the probability to reveal the biomarker D-R in Ph1 trial.

References: