Using HuTrial™ To Aid Predicting Response in a Patient Population

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INTRODUCTION

One of the biggest challenges in drug discovery is directing drug treatment to the correct population of patients. The CrownBio collection of patient-derived xenograft (PDX) models – HuPrime® currently counts more than 2,500 models over more than 70 indications. These human surrogate mouse models, are reflective of the diversity of genetics, tumor heterogeneity, and response to therapy observed in the patient population. HuPrime models are searchable in HuBase™, CrownBio’s curated database including gene expression, copy number, mutational analysis as well as patient clinical data comprising diagnosis, pathology, and IHC information. The vast number of models available allows researchers to perform surrogate Phase II-like trials, utilizing one patient sample per tumor bearing animal per treatment group (n=1 studies). In this study we show reproducibility of n=1 studies comparing to traditional preclinical mouse studies consisting of multiple animals grafted with the same tumor and treated with the same test agent. Furthermore, we show that the use of one patient sample per treatment allows the expansion of the study, utilizing samples from multiple patients, thereby reducing the cost of preclinical studies. HuPrime models can be leveraged to discover biomarkers, identify patient responder and non-responder profiles to accelerate drug development and improve chances of success in the clinic.

STUDY DESIGN

27 SCLC and 18 NSCLC PDX models were evaluated in this study. Tumors were inoculated subcutaneously in the rear flank of NOD-SCID mice. For each model, 1 animal served as control and 1 animal was treated with standard of care (SoC) agents. For validation of the n=1 SCLC study, we evaluated 4 models in a n=5 per group format. Tumor volume and body weight measurements were taken 3 times a week for all studies.

MODEL INFORMATION

SUMMARY

- HuTrial study designs utilizing an n=1 approach as shown here are a translational means of evaluating therapeutics in HuPrime SCLC and NSCLC models before entering the clinic.
- These study designs offer an efficient method to provide confident preclinical rationales for clinical development strategies that include selection of appropriate patient population, identification of appropriate biomarkers and combination therapies.

RESULTS

Figure 1 (left): Representative SoC-sensitive (left panel) and SoC-resistant (right panel) models for SCLC and NSCLC indications. Cisplatin was administered on Day 1 and etoposide on Days 1,2,3.

Figure 2 (right): Waterfall plot for n=1 SoC R5 in SCLC and NSCLC models. Data plotted as %ΔT/ΔC. A wide response range was observed in both indications.

Figure 3 (left): Model validation by comparing n=1 (left panels of the pair) versus n=5 (right panels of the pair) study in 4 SCLC models. Response observed in n=1 screen is confirmed in n=5 validation study.