# Parameters influencing design of mouse clinical trial (HuTrial™)

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## Introduction

Patient-derived xenograft (PDX) is increasingly used to evaluate oncology drug. The fast accumulation of PDXs enables performing randomized, controlled and statistically powered mouse clinical trials (MCT, or HuTrial™) in a cost-effective and streamlined way. We hereby attempt to discuss general trial design (Fig. 1) and the parameters influencing it.

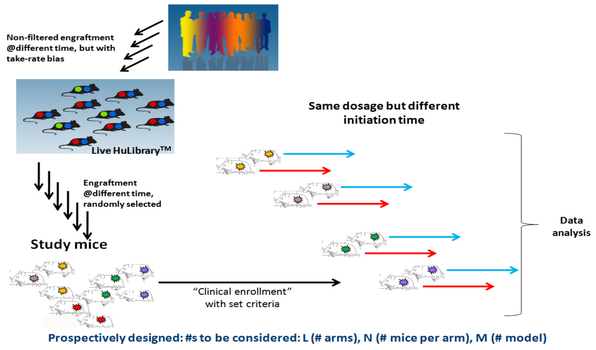


**Fig. 1. MCT workflow and study design**

## How many mice are needed?

- 10-mice per arm is commonly used (e.g. 10 in vehicle and 10 in treatment group or "10:10" format).
- Common endpoints: 1) tumor volume ratio, or ΔT/ΔC, or 2) Tumor Growth Inhibition (TGI).
- In an MCT of 40 PDXs with 10:10 design, a simulation by randomly drawing *n* (1≤n≤ 9) mice from both groups for each PDX was performed. The deviation of ΔT/ΔC from that in the 10:10 design was calculated, which was repeated 1000 times to generate distributions of ΔT/ΔC difference (Figure 2).
- Findings: (1) ΔT/ΔC difference has quite large variation in the 1:1 design, and quickly decreases when more mice are added for each PDX model; (2) for the same n:n design, ΔT/ΔC difference is smaller for more potent drugs on the same set of PDX models.

## Influence of tumor growth rate

Next we asked whether growth rate of PDX difference impacts drug efficacy readout. We used an exponential growth model to estimate tumor growth rate (control)

$$TV_d = TV_0 e^{kd}$$

where $TV_0$ is the initial tumor volume, $TV_d$ is the tumor volume at $d^{th}$ day after dosing starts, $k$ is the rate constant. Tumor volume doubling time was then calculated using $k$.

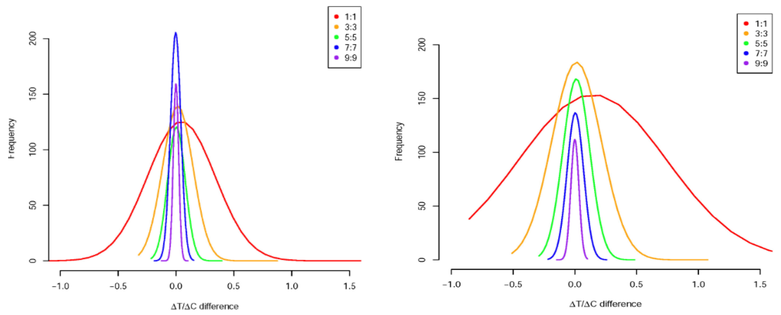


**Fig. 2. ΔT/ΔC difference between 10:10 and n:n study designs for (Left) a potent drug and (Right) a less potent drug.**

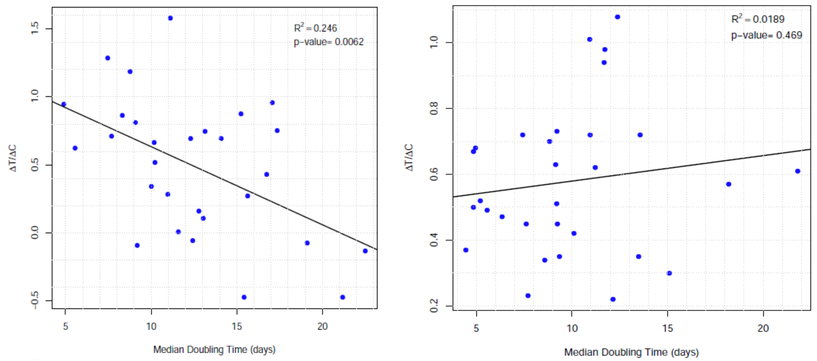


**Figure 3. (A) A weak correlation between tumor growth rate (measured by tumor volume doubling time in control groups) and ΔT/ΔC was observed, where ΔT/ΔC value is inflated in tumors with fast growth (short doubling time) It is thus necessary to normalize ΔT/ΔC values to reduce the bias caused by different growth rates. (B)On the other hand, such adjustment is certainly unnecessary if the correlation is not detected, as observed in other MCTs.**

## Conclusions

1. Many parameters can influence MCT design;
2. The # of mice per arm could be influenced by the drug potency (e.g. HR, TGI) and by # of models used;
3. The trial endpoints can be objective response (e.g. T/C, TGI) and "survival" (e.g. MST, HR, ..), as seen in the clinic.
4. There seems no correlation between efficacy readout and tumor growth (except minor influence on TGI);
5. Clinical response definition of RECIST criteria can also be adopted in MCT, so to mimic clinical trial closely..

## Survival endpoint

Survival endpoint, analogous to that in human trials, was also investigated. First, the event, e.g. tumor volume threshold (e.g., 800mm$^3$), was defined. Then time-to-event for each mouse using either the exponential growth model or local linear interpolation on tumor volumes was estimated. Censoring can be applied, if the event cannot be reached (e.g. death due to drug toxicity, etc.) (Fig. 4A).

Using the dataset in Fig. 3A, we obtained median survival time (MST) estimates in vehicle groups and treatment groups (Fig. 4B), which are highly correlated. Treated PDXs on average exhibit longer MST (27.2 days) than untreated (23.2 days), a 17% improvement. For each PDX model, if there are sufficient number of mice in the vehicle group and the treatment group, we can also compute a hazard ratio (HR), as is the case in this exemplar dataset. We found that HR is not correlated with tumor growth rate (Fig. 4C), but strongly correlated with ΔT/ΔC, thus can be used for quantifying drug efficacy (Fig. 4D).

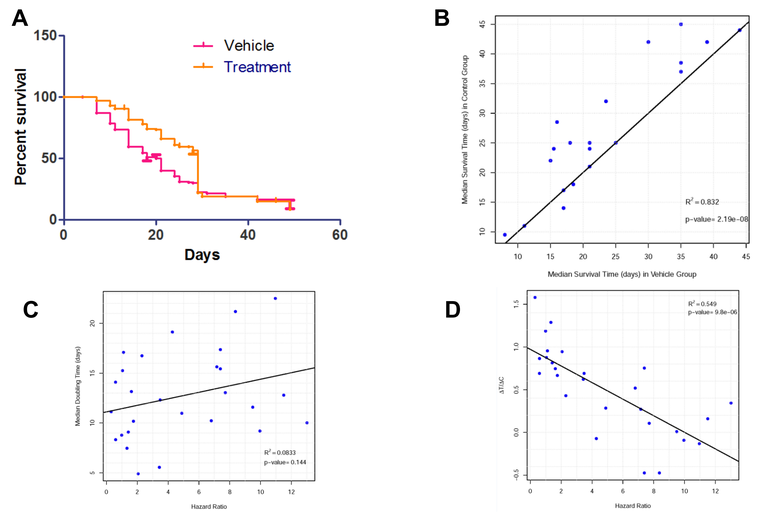


**Fig. 4. Survival analysis of MCT data in Fig. 3A. (A) Survival curves of mice in vehicle and treatment groups. (B) MST for mice in vehicle and treatment groups of 20 PDXs. The line is not the linear regression line but one with zero intercept and unit slope. (C) HR vs. median doubling time. (D) HR vs ΔT/ΔC. $R^2$ and *p*-value are computed based on a linear regression of the two variables.**

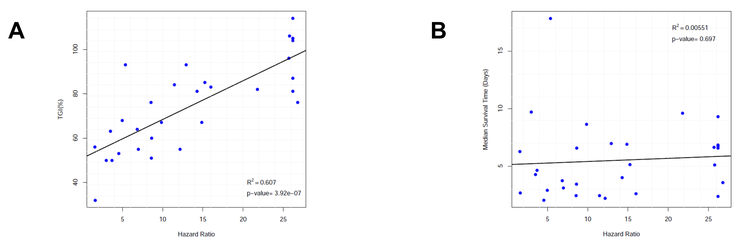


**Figure 5. Survival analysis of MCT data using RECIST criteria. Event can be defined according to the RECIST criteria (JNCI, 3: 205): a model is in progression free survival (PFS) before reaching 173% of its initial tumor volume. Findings: HR is correlated to TGI, but not tumor growth rate (Fig. 5), indicating that HR is a better measurement of drug efficacy than TGI.**