Preclinical Mouse Trials (MCT) to Guide the Human Studies

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Abstract

Background: Patient-derived xenograft (PDX) tumor models are widely used for assessing cancer treatments, due to their strong similarity to the original patient histo- and molecular pathology, as well as their predictive power. A comprehensive PDX library is reflective of the original patient diversity. Mouse clinical trial (MCT) using cohorts of PDXs may potentially be used to guide human clinical trial.

Methods: We previously described the generation of a cohort of NSCLC PDXs (~now nearly 300)[1]. Here we randomly enrolled PDX models from this panel in a MCT to assess the efficacy of an investigational antitumor agent, as compared with standard of care (SoC) compounds, using a variety of clinically relevant endpoints[2] (ΔT/ΔC, RECIST, OS, PFS). Our MCT results provide a valuable guide for the clinical development of this new anticancer agent.

Results: In the present study we investigated the efficacy of an experimental agent on a cohort of randomly selected NSCLC models. This novel compound showed superior activity when compared to cisplatin or paclitaxel in the same subject cohort, with no additive effects with either of the two drugs, suggesting its use as 1st line treatment or possibly a 2nd line development strategy in patients with recurrent disease following SoC treatment. Although both cisplatin and paclitaxel performed better than control on this PDX cohort (medium PFS: 41 days for paclitaxel, 37 days for cisplatin and 28 days for placebo; p-values 0.001 and 0.03, as compared to placebo, respectively), no statistically significant difference was observed between the two (p-value of 0.47). OS analysis led to the similar observation (medium OS of 95, 67 and 41 days, respectively, p-value <0.001, 0.002 and 0.23 in the same order). Further analysis revealed that response to SoC treatment does not correlate among PDXs enrolled in the study, suggesting that:

1) subjects resistant to one of the agents (e.g. 1st line treatment) might still respond to the other (2nd line treatment);
2) combination of the two SoC agents is a reasonable strategy.

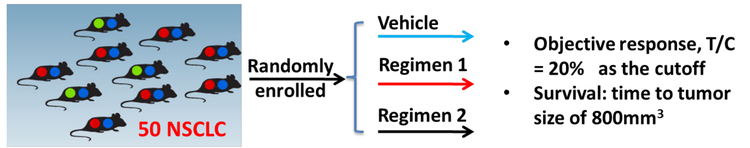
Since our PDX models have been genomic-profiled, it is possible to utilized them to identify markers predictive of response.

1. Yang, M., *et al. Int J Cancer* **132**, E74-84 (2013)
2. Zhang, L., et al. Sci Rep. 3:2992 (2013)

Trial Objectives

1. **Demonstrate anti-tumor activity of a new agent in NSCLC**
2. **Establish dosing strategy**
3. **Provide human clinical development strategy**

Trial Design



Trial Results

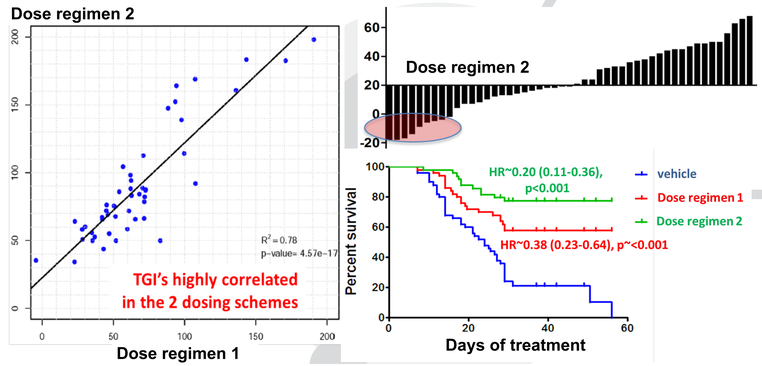


Figure 1. A novel immunotherapy agent shows anticancer activity in NSCLC. Dose regimen 2 has superior efficacy. A subset of models display high sensitivity (shrink or T/C<0).

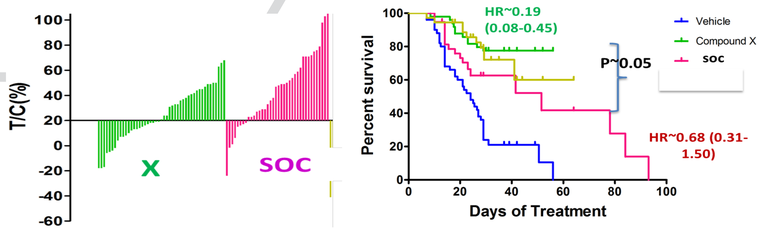


Figure 2. Comparison with SoC, implicating a 1st line treatment development strategy.

Trial Results

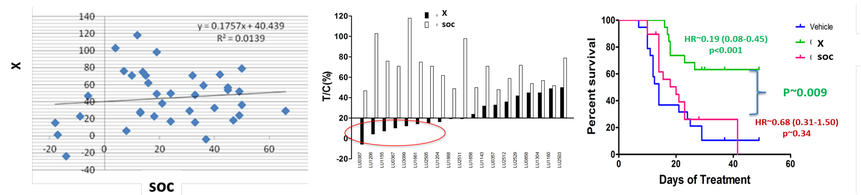


Figure 3. The SoC resistant population is responsive the the new experimental agent, suggesting a 2nd line treatment development strategy.

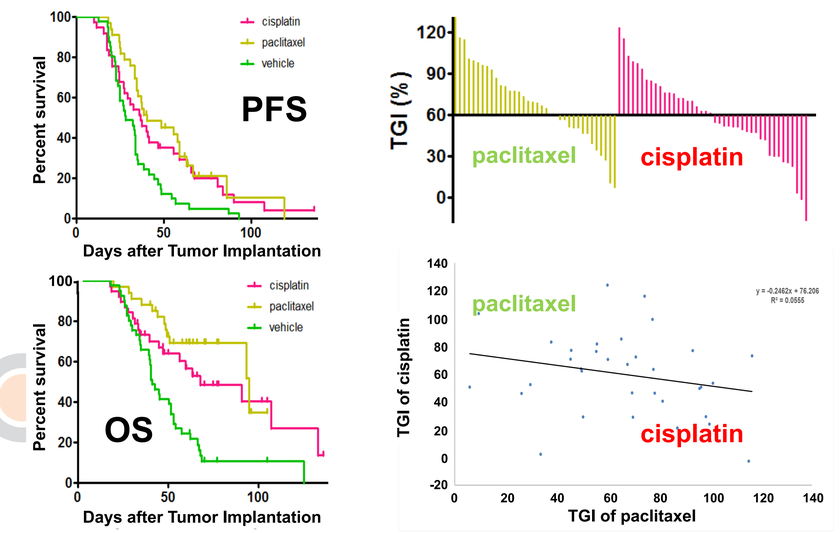


Figure 4. Overall response, PFS, OS, and efficacy correlation for paclitaxel *vs.* cisplatin treatment in a cohort of NSCLC PDX.

Conclusions

1. **A new experimental immunotherapy shows strong efficacy on a randomly selected subcohort of PDX NSCLC models. Two regimen were tested with regimen 1 performing better than regimen 2.**
2. **Superior efficacy of new agent compared to SoC, suggests a possible 1st line development strategy.**
3. **SoC resistant population is sensitive to experimental agent, suggesting a possible 2nd line development strategy.**
4. **Taxol and cisplatin have similar not overlapping activity. They can be used together, either in combination or sequentially.**
5. **MCT is an effective approach to help selecting indication and guide clinical development strategy.**