# Analysis of patient derived xenograft studies in Oncology drug development: impact on design and interpretation of future studies

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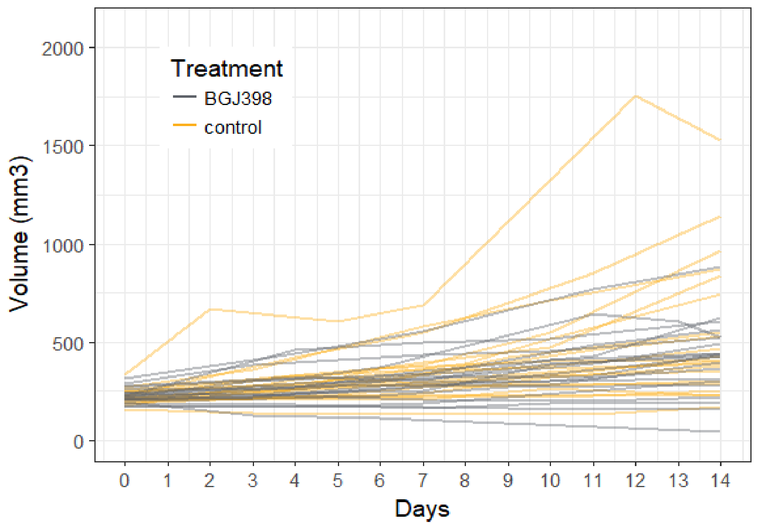
## Summary

Preclinical Oncology drug development is heavily reliant on xenograft studies to assess the anti-tumour effect of new compounds. Patient derived xenografts (PDX) have become popular as they may better represent the clinical disease, however variability is greater than in cell-line derived xenografts. In this study we compare the typical approach of analysing these studies, t-test of final volumes, to a model based approach across 59 2-arm trials from a Novartis PDX database[1].

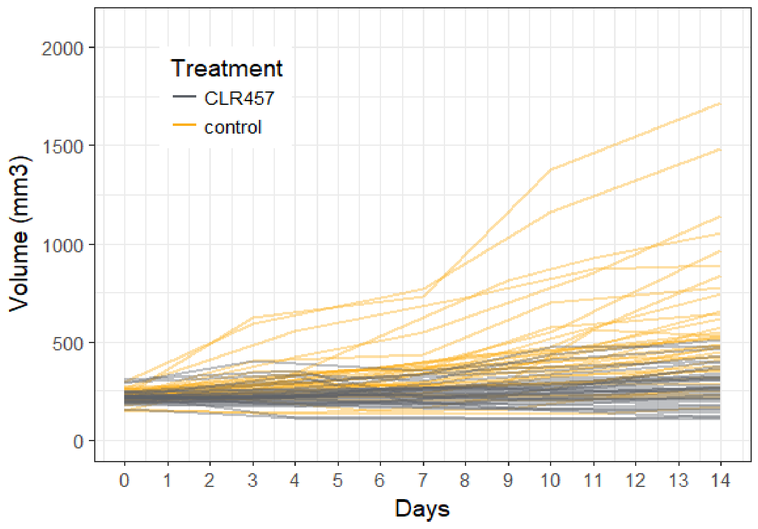
**Key Result: model-based approach has significantly more power than simply applying a t-test on final volumes.**

Application of a model-based analysis should allow studies to use less animals and run experiments for a shorter period thus providing effective insight into compound anti-tumour activity.

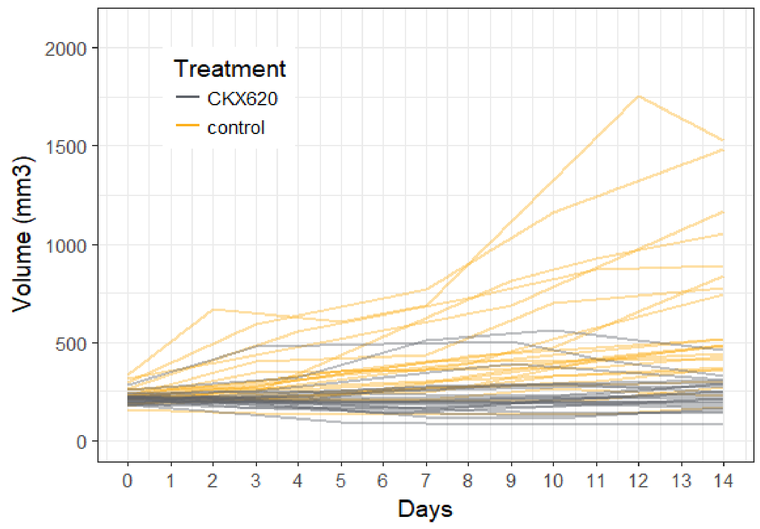
## Examples extracted from Novartis PDX database




Tumour Growth Inhibition (TGI) = 41%
t-test p-value = 0.134
Model-based p-value <0.001




Tumour Growth Inhibition (TGI) = 85%
t-test p-value <0.001
Model-based p-value <0.001



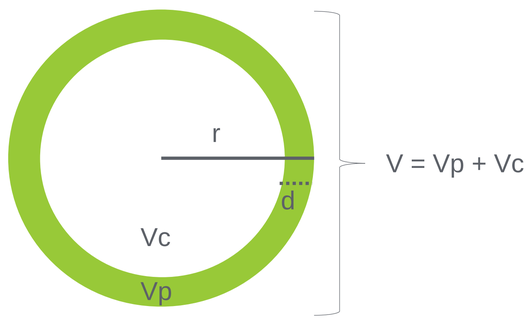

Tumour Growth Inhibition (TGI) = 98%
t-test p-value <0.001
Model-based p-value <0.001

## Data / Methods / Model

**Data**: Extracted from a PDX drug treatment database released by Novartis[1] (Examples shown above).

**2-arm trials:** Percent tumour growth inhibition (TGI) at two time-points, day 10 and day 14 was calculated for all 59 2-arm trials.

**Analysis:** For each trial, the treatment effect was calculated using an un-paired t-test and also via a model-based (linear mixed-effects) analysis using a semi-mechanistic tumour growth model[2] (shown on right): p-value derived from the likelihood ratio-test). A comparison of p-values was then conducted.




r = tumour radius
d = depth of proliferating rim

V = total volume of tumour
Vp = volume of proliferating rim
Vc = volume of hypoxic/necrotic core

$V = (4/3)\pi r^3$
$V_c = (4/3)\pi(r-d)^3$
Since $d \ll r$
$V_p = V - V_c \approx 4\pi r^2 d$

**Derivation of Radius Linear Law[2]:**
Assume proliferating rim has thickness d, small relative to radius r, grows at rate a, volume is approximately:

$$V_p = 4\pi r^2 d$$

growing at a rate

$$\frac{dV_p}{dt} = aV_p = a4\pi r^2 d$$

growth equation for the radius is given by

$$\frac{dr}{dt} = \frac{dr}{dV}\frac{dV}{dt} = \left(\frac{1}{4\pi r^2}\right) a4\pi r^2 d = ad$$

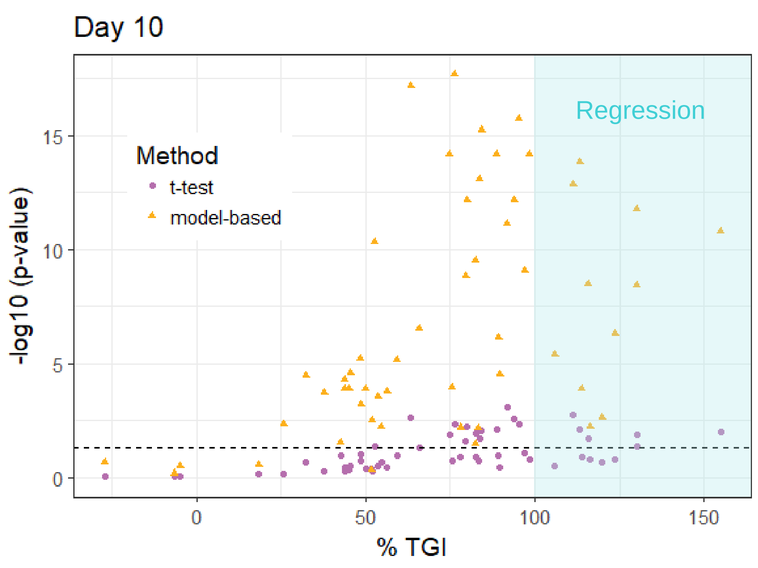
which is solved to give the linear equation

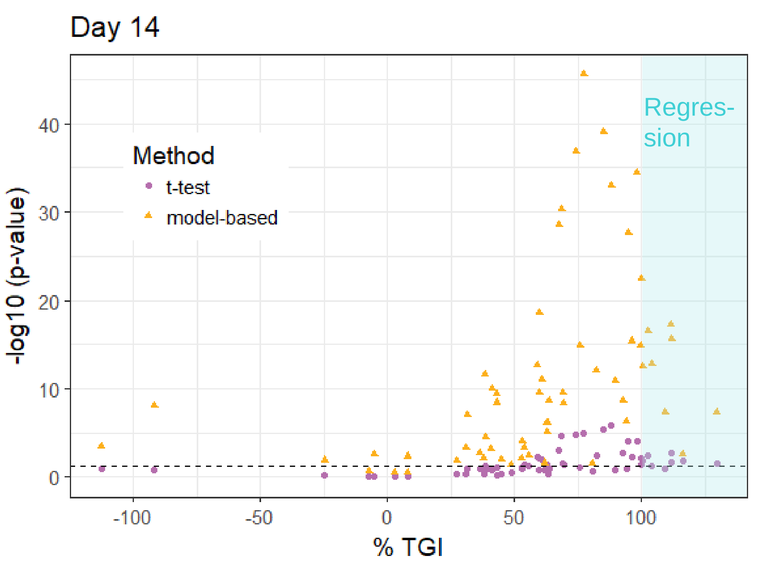
$$r = R_0 + adt$$

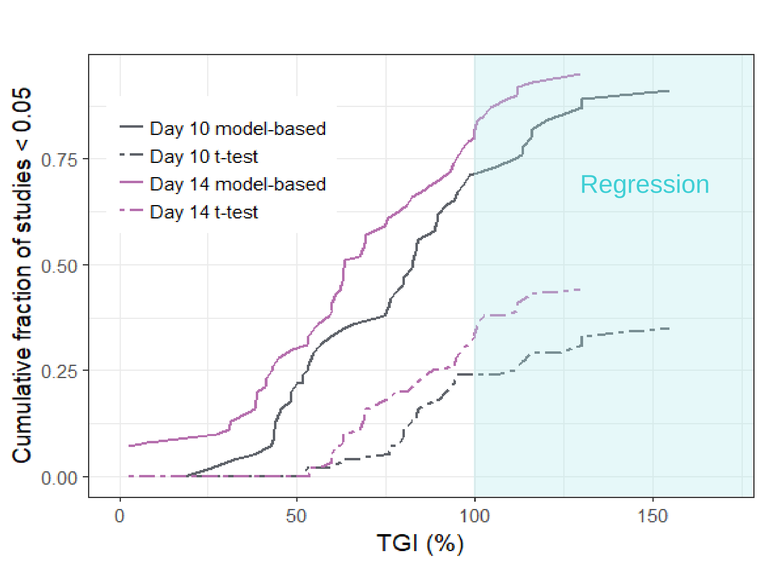
$R_0$ is initial radius, ad is replaced by constant *c*.

## Results

We found that the model-based analysis had greater statistical power than the un-paired t-test approach. In particular we found the model-based approach was able to detect TGI values as low as 25 percent whereas the un-paired t-test approach required at least 50 percent TGI. When data was analysed over 14 days, using the model based approach, 95% of results were statistically significant, compared to 91% when day 10 data was used.




## Conclusion

The analysis of 59 2-arm patient derived xenograft studies highlighted that taking a model-based approach gave increased statistical power over simply performing an un-paired t-test on the final study day. Importantly the model-based approach was able to detect smaller size of effect compared to the un-paired t-test approach which maybe common of such studies. Application of a model-based analysis should allow studies to use less animals and run experiments for a shorter period thus providing effective insight into compound anti-tumour activity.

**References:**
1) Gao et al. High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. Nat Med. 2015 Nov; 21(11):1318-25
2) Mistry et al. Model based analysis of the heterogeneity in the tumour size dynamics differentiates vemurafenib, dabrafenib and trametinib in metastatic melanoma. CCP 2018 Feb; 81(2) 325-32

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