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.

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

Data: Extracted from a PDX drug treatment database released by Novartis1 (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 model2 (shown on right): p-value derived from the likelihood ratio-test. A comparison of p-values was then conducted.

Data / Methods / Model

Derivation of Radius Linear Law2:

Assume proliferating rim has thickness d, small relative to radius r, grows at rate a, volume is approximately:

\[ V_p = 4\pi r^2d \]

growing at a rate

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

growth equation for the radius is given by

\[ \frac{dr}{dt} = \frac{dV_p}{dV} \frac{dV}{dt} \]

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:

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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