

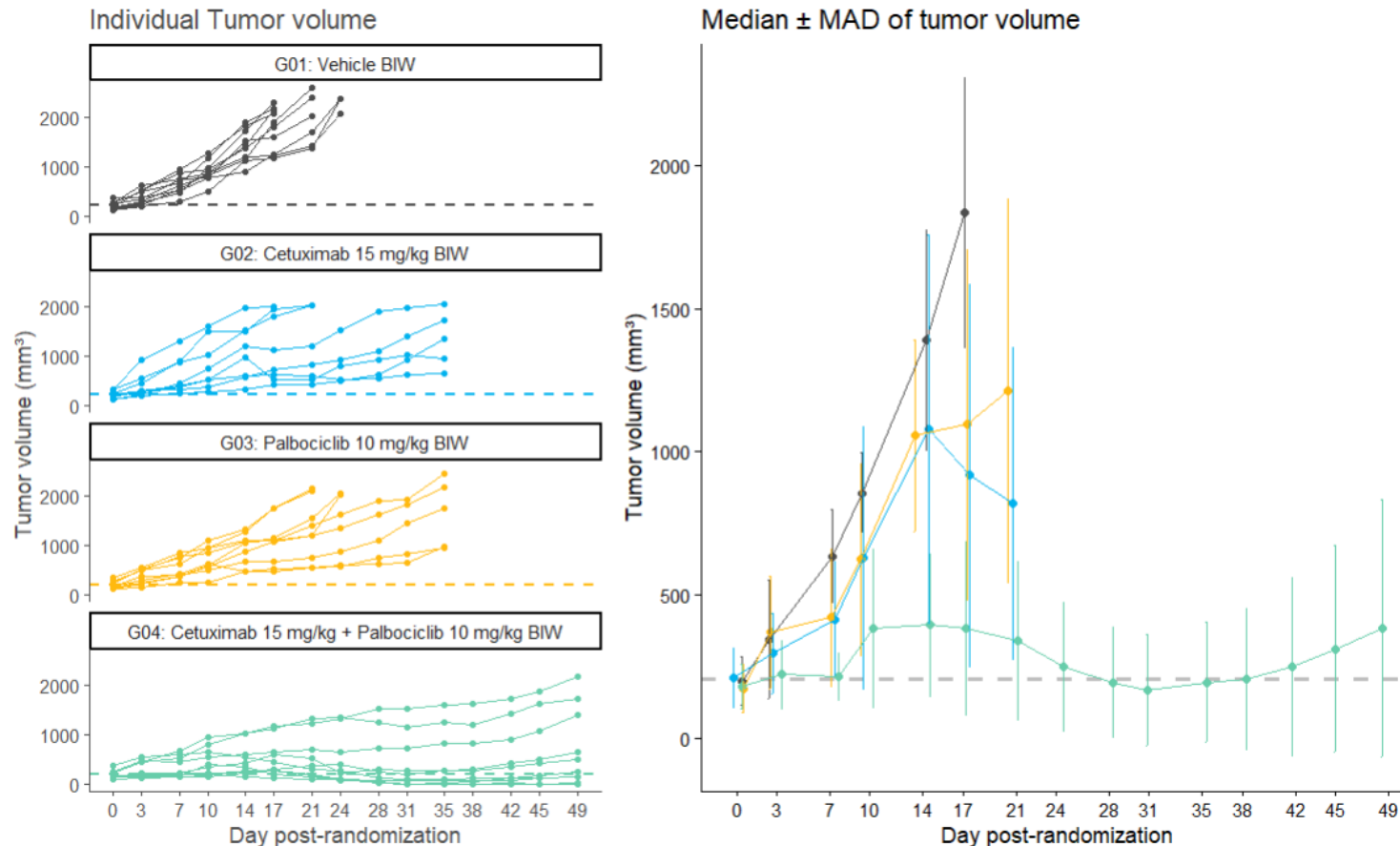
Flexible Modeling of Repeated Tumor Volume Data Using Generalized Additive Mixed Models.

Odile Coudert Berthion

23/09/2026

Evaluation of the combination of Cetuximab and Palbociclib in a colon patient-derived xenograft mouse model

The tumor volume is measured for each animal twice a week



Statistical model:

- ✓ Repeated Anova
- ✓ Non-Parametric Anova-Type
- ✓ Linear Mixed Model after log Transformation
- ✓ Growth models (Gompertz...)
- ✓ GAMM

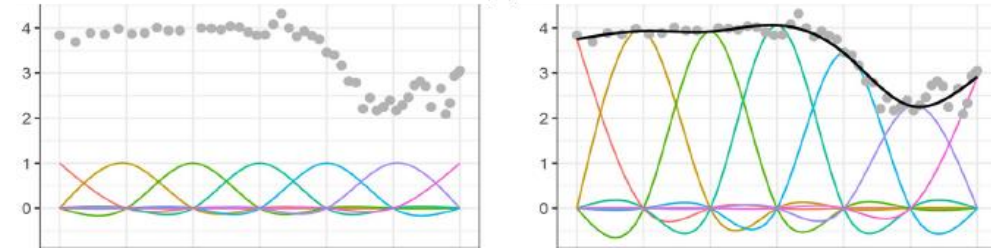
GAMM: Generalized Additive Mixed Model

Inclusion of splines in the model

- A spline is the sum of K basis functions b_k to which coefficients β_k are

applied:

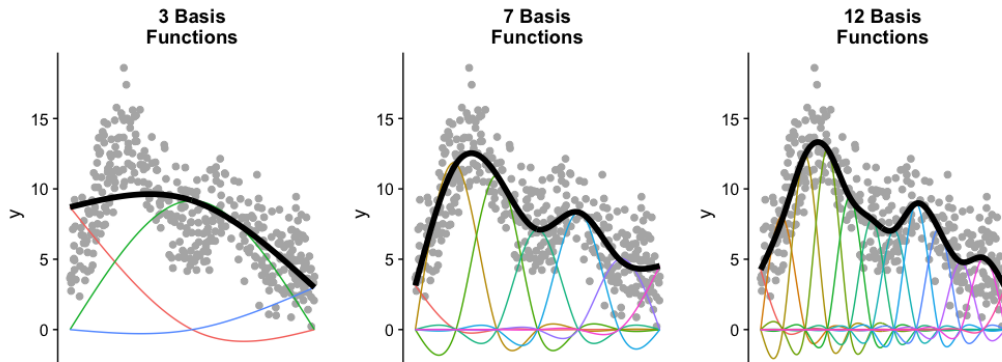
$$f(x) = \sum_k^K \beta_k b_k(x)$$



Splines: basis functions are applied to obtain a smooth curve

- The wiggleness (=complexity of the curve: how the curve changes shape) can be controlled:

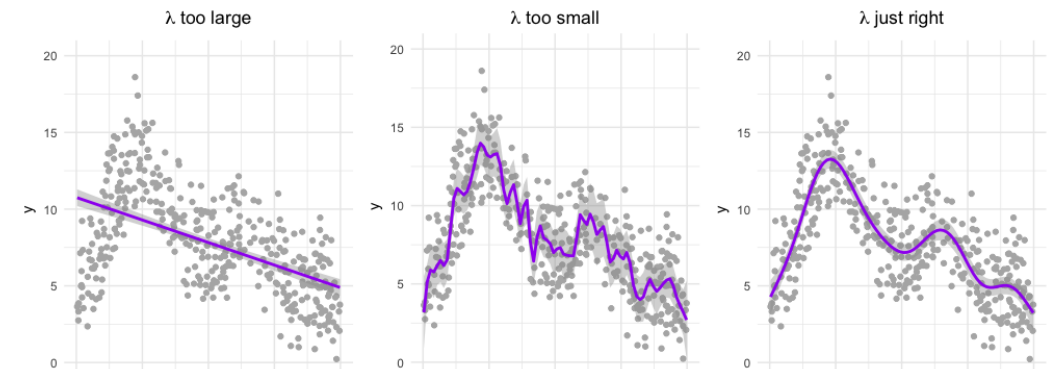
- Through K the number of basis functions



- Through the smoothing parameter λ

Penalized likelihood estimated in the model:

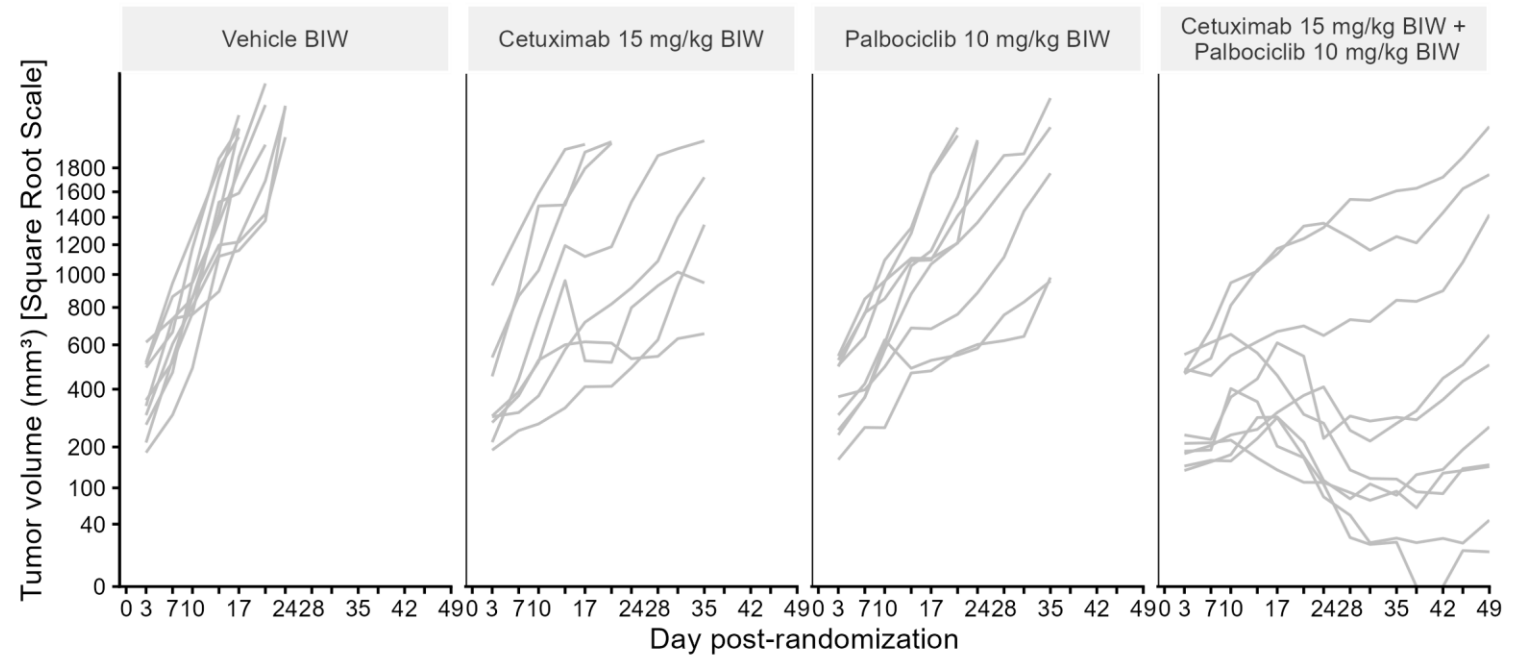
$$\text{likelihood} - \lambda * \text{wiggleness}$$



Writing of a GAMM using **mgcv** R package

```
gam(sqrtTV ~  
  baseSQRT + trtGroup +  
  s(day, bs="cr")+  
  s(day, by= trtGroup, bs="cr") +  
  s(day, animalID, bs="fs", xt="cr", m =2),  
  family = gaussian(link = "identity"),  
  data = , method = "REML")
```

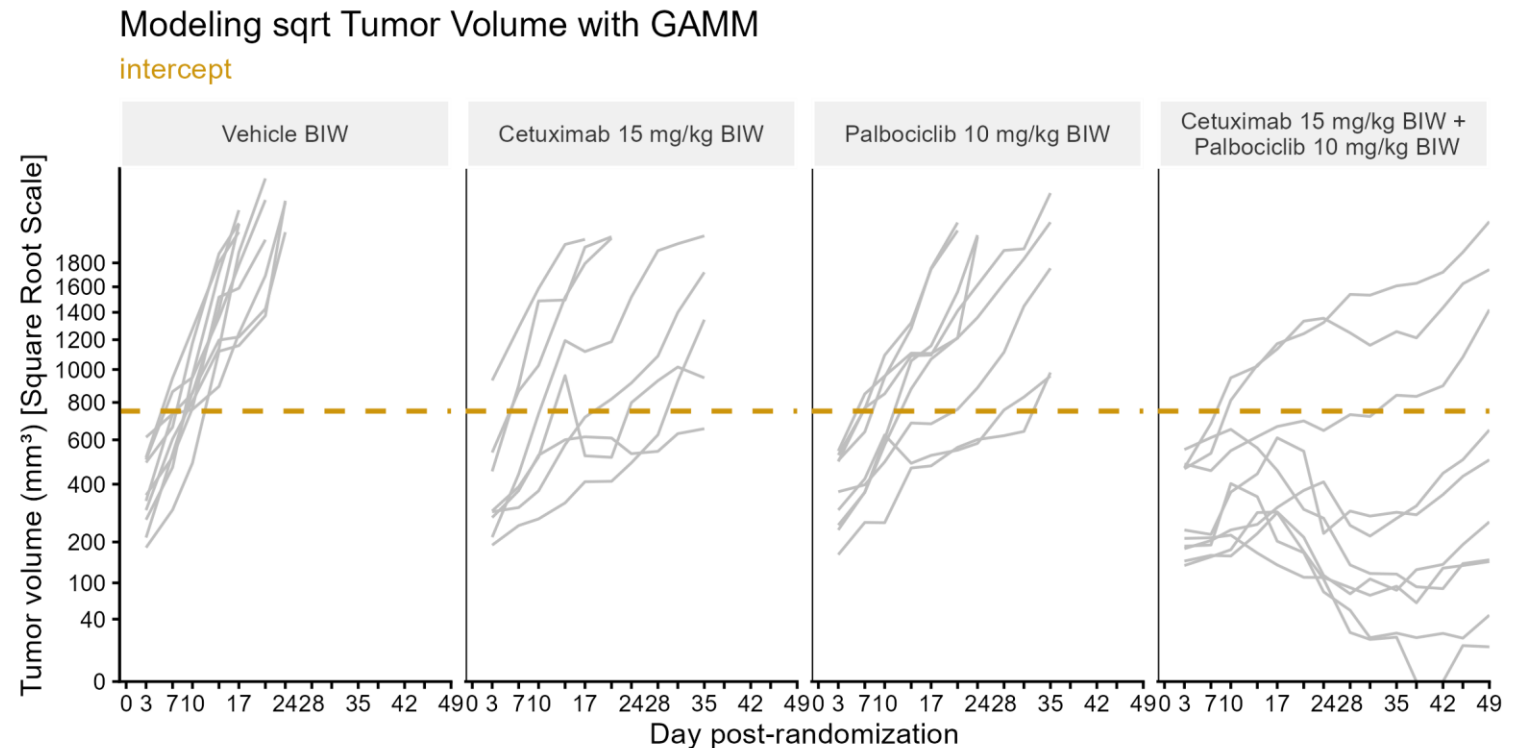
Modeling sqrt Tumor Volume with GAMM



Writing of a GAMM using **mgcv** R package

Linear effects

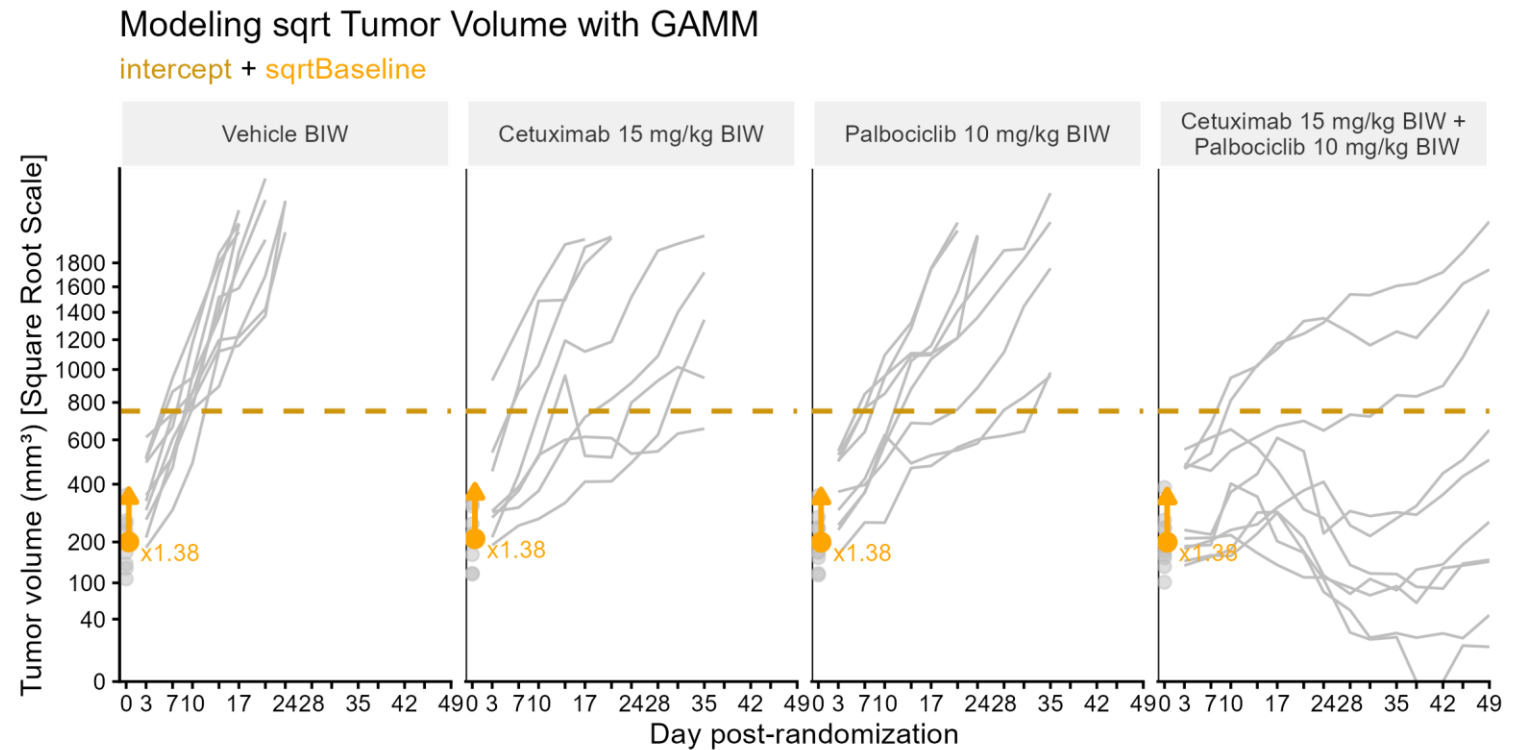
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Writing of a GAMM using `mgcv` R package

Linear effects

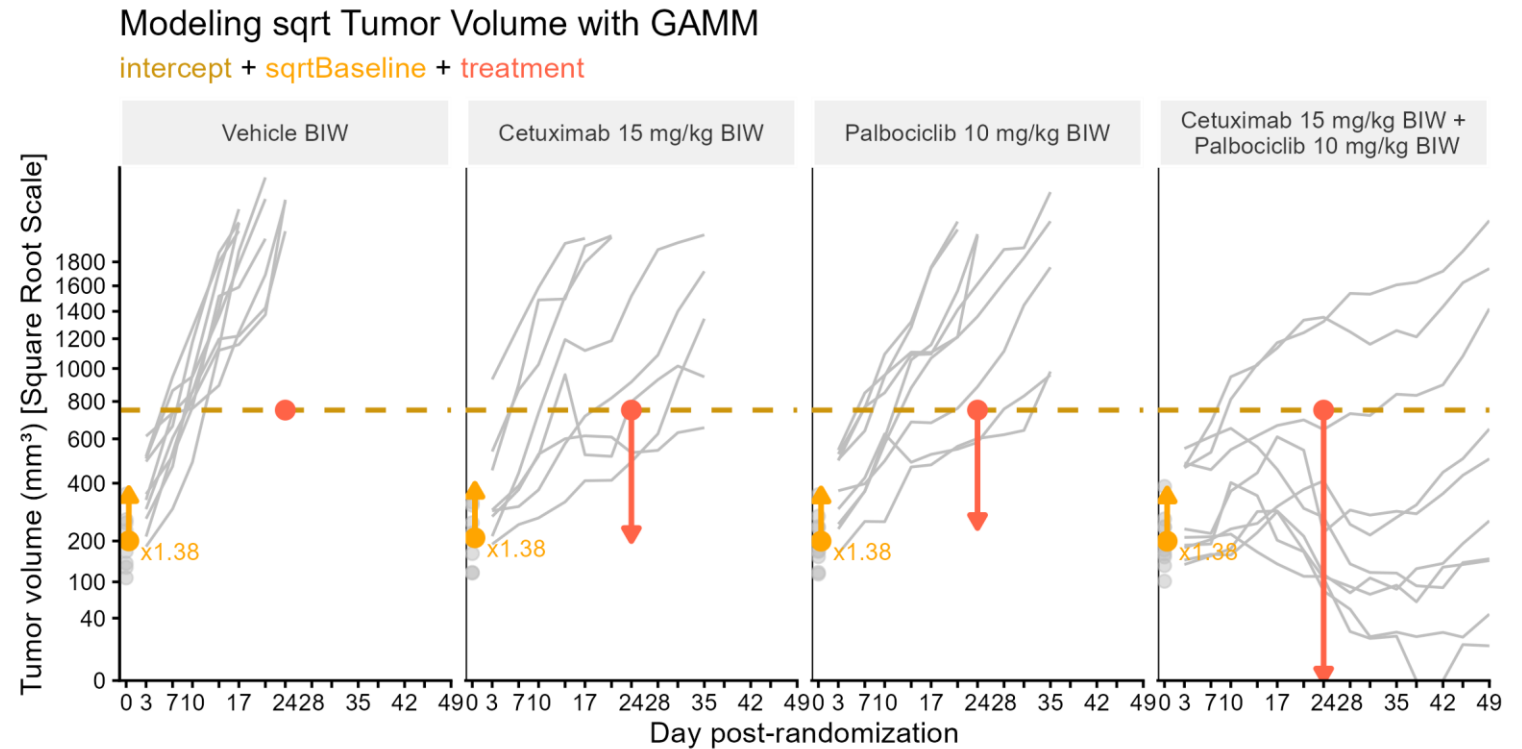
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```



Writing of a GAMM using **mgcv** R package

Linear effects

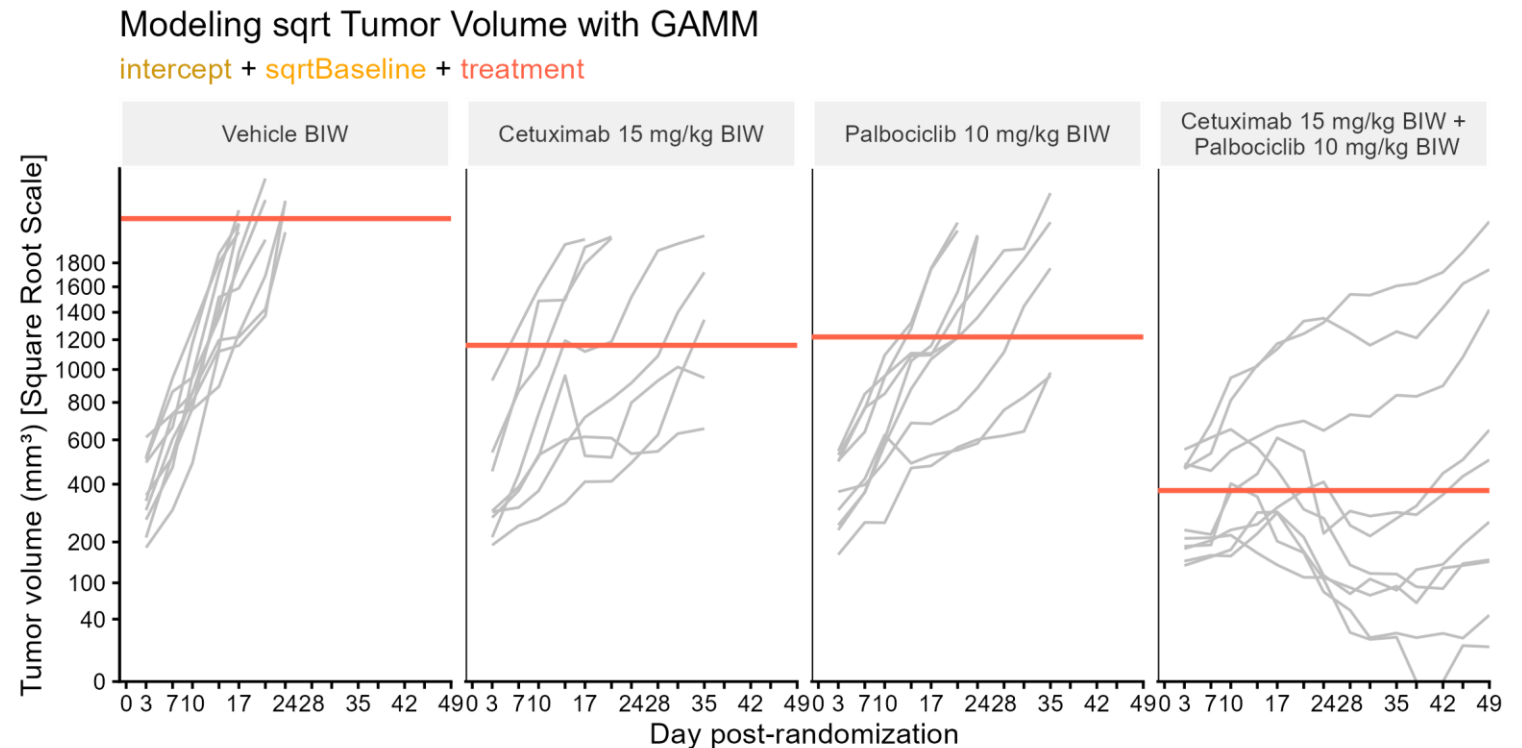
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gam(sqrtTV ~  
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Writing of a GAMM using **mgcv** R package

Linear effects

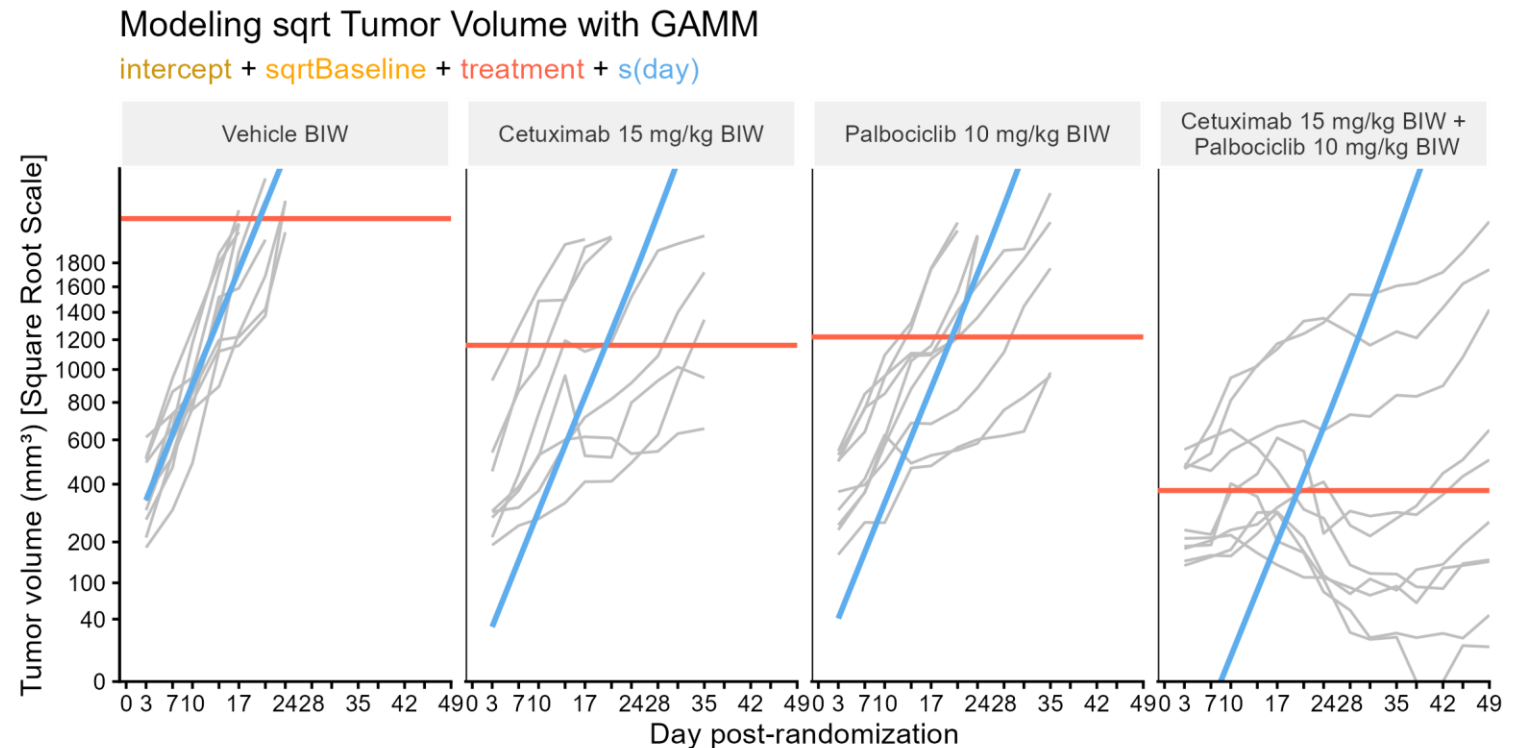
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gam(sqrtTV ~  
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  s(day, animalID, bs="fs", xt="cr", m =2),  
  data = , method = "REML")
```



Writing of a GAMM using **mgcv** R package

Linear effects, cubic spline effects

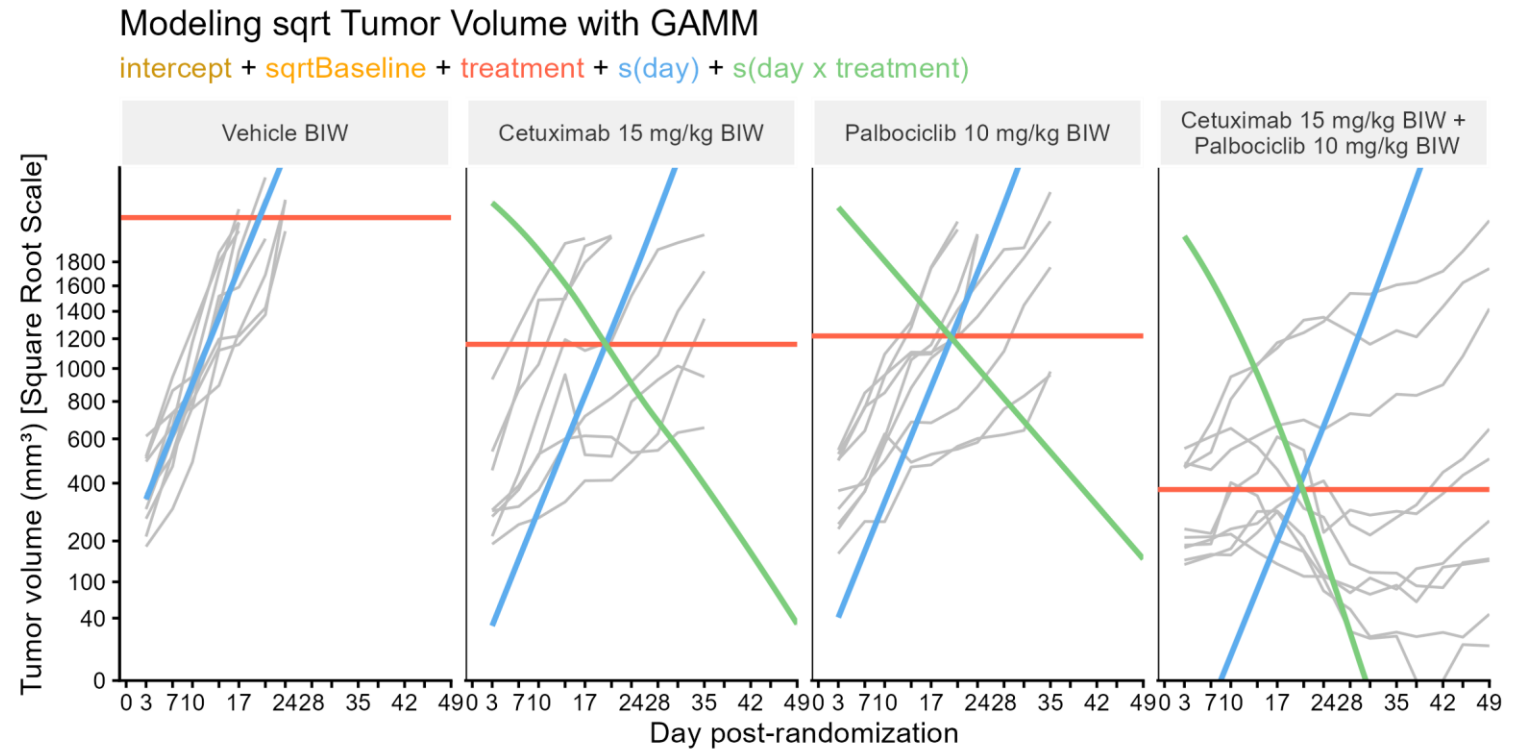
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  baseSQRT + trtGroup +  
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Writing of a GAMM using **mgcv** R package

Linear effects, cubic spline effects

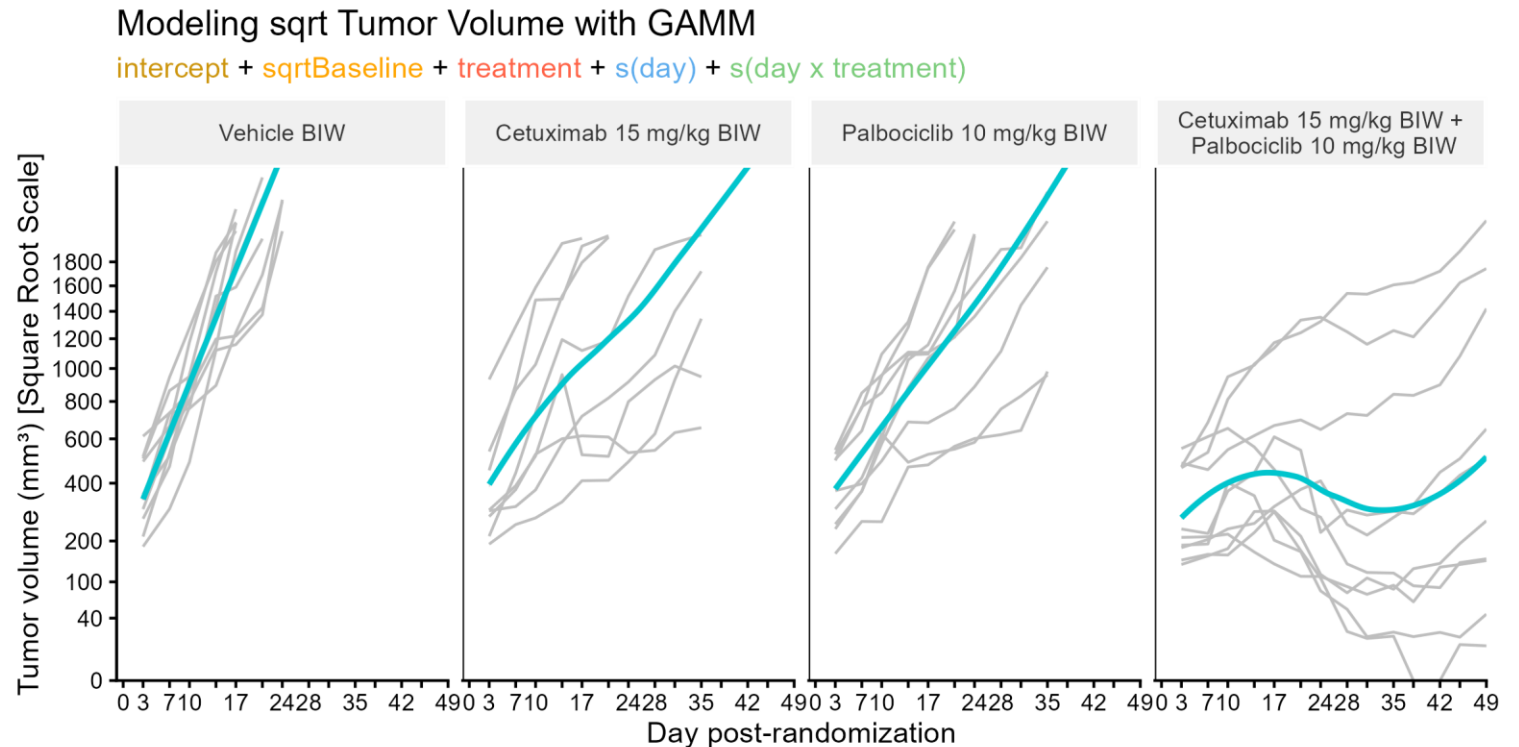
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Writing of a GAMM using **mgcv** R package

Linear effects, cubic spline effects

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  s(day, by= trtGroup, bs="cr") +  
  s(day, animalID, bs="fs", xt="cr", m =2),  
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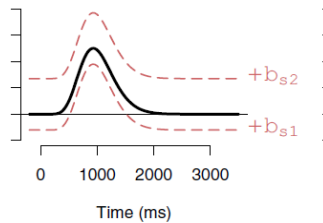


Writing of a GAMM using **mgcv** R package

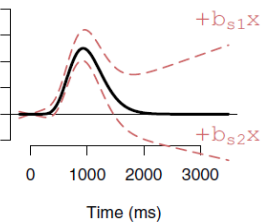
Linear effects, cubic spline effects, random cubic spline effects

```
gam(sqrtTV ~  
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  s(day, bs="cr")+  
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  s(day, animalID, bs="fs", xt="cr", m =2),  
  data = , method = "REML")
```

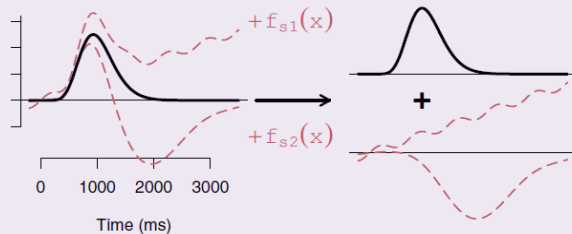
Random intercept



Random slope

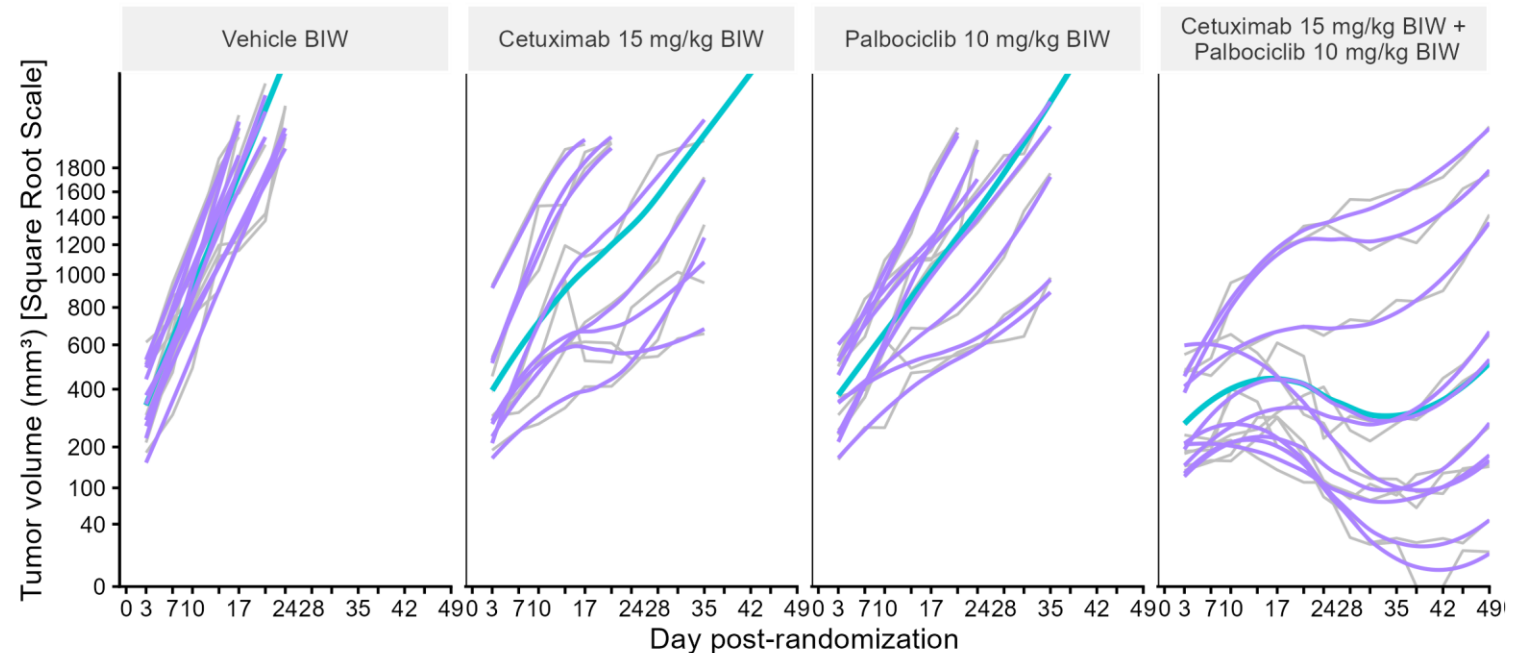


Random smooths



Modeling sqrt Tumor Volume with GAMM

intercept + sqrtBaseline + treatment + s(day) + s(day x treatment) + random s(day: animalID)



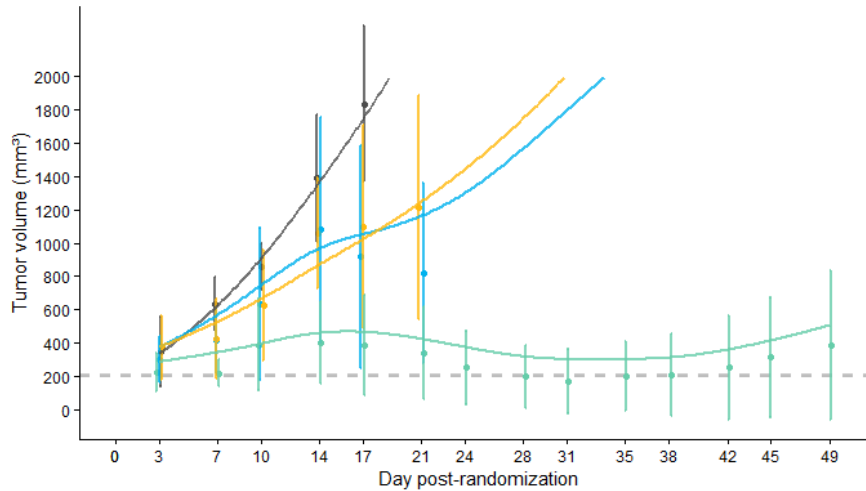
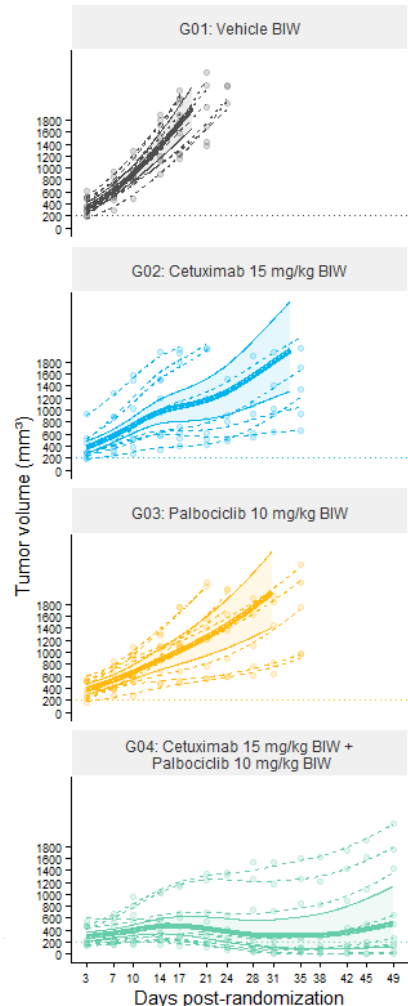
Inferences with GAMM

Use of simultaneous confidence intervals and derived 'pvalues'

Effect of the combination of Cetuximab and Palbociclib on BALB/c mice bearing CR1197 tumor model

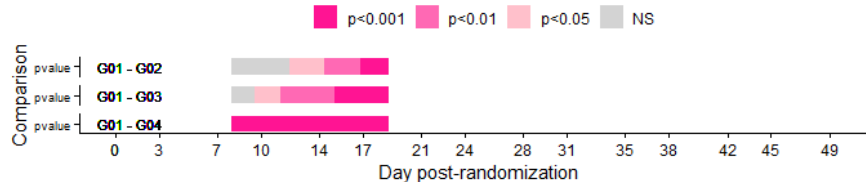
Group GAMM Fit with 95% CI and Individual GAMM Fit (---)

Gamm fit and Median $\pm$ MAD of tumor volume



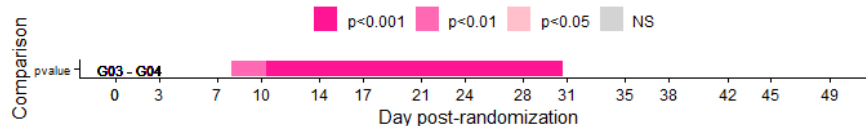
Objective 1: comparison of the treated groups to the vehicle group

Hommel adjusted pvalues from simultaneous tests



Objective 2: comparison of the combination to the best single agent

Pvalues from simultaneous tests



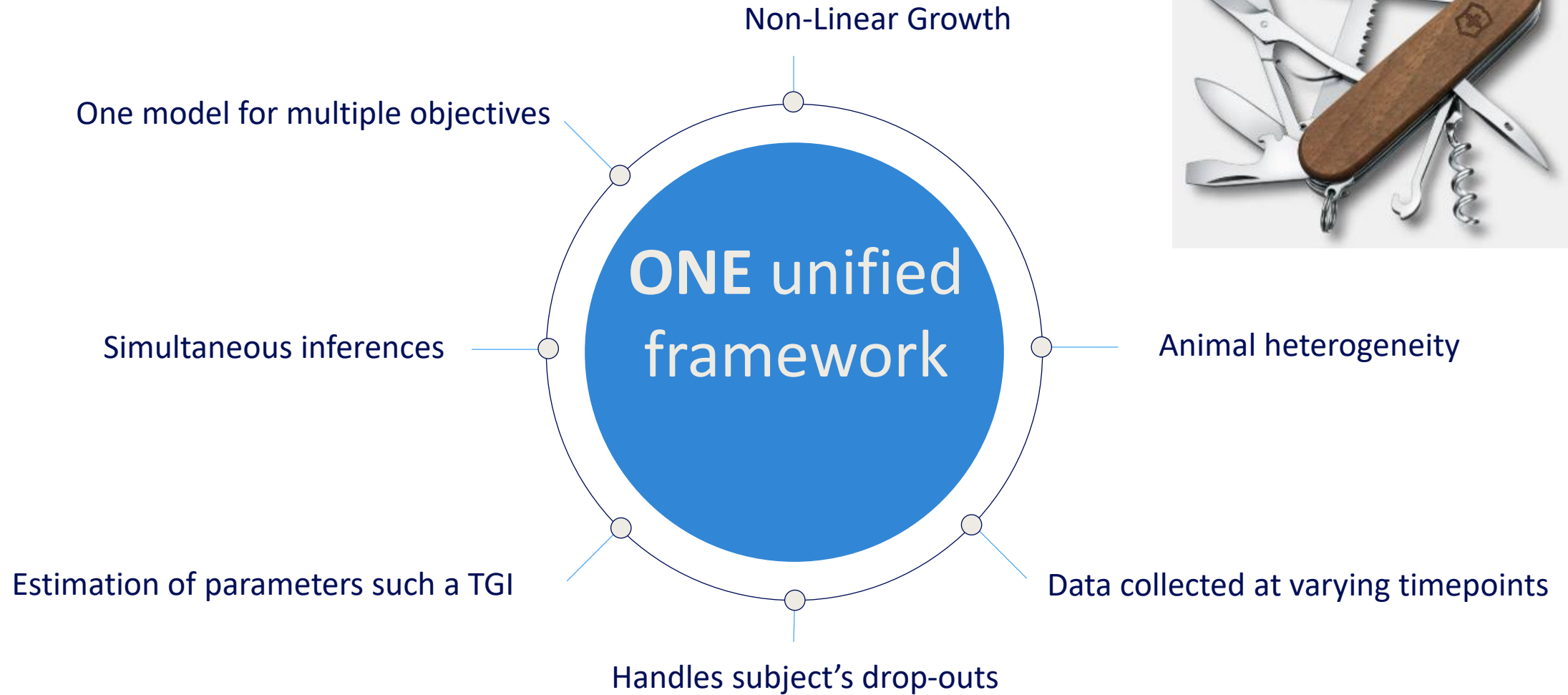
Treatment group
• G01: Vehicle BIW
• G02: Cetuximab 15 mg/kg BIW
• G03: Palbociclib 10 mg/kg BIW
• G04: Cetuximab 15 mg/kg + Palbociclib 10 mg/kg BIW

Inferences:

- ✓ Estimation of the mean effect in each group and of their difference **on a specified time interval**
- ✗ Pointwise confidence intervals only control the alpha risk on average
- ✓ **Simultaneous confidence intervals** come from posterior predictions and control the alpha risk at 5 % on the entire time interval.
- ✓ **PSimBas** can be derived as pvalues (Probability Simultaneous Band Scores) ¹
- ✓ Answer additional issues: estimation of the Tumor Growth Inhibition, of the time of regression or tumor relapse, of the tumor doubling time, of a combination index...

[1]: Meyer, M.J., Coull, B.A., Versace, F., Cinciripini, P. and Morris, J.S. (2015), Bayesian function-on-function regression for multilevel functional data. Biom, 71: 563-574. <https://doi.org/10.1111/biom.12299>

Why GAMM?



Non exhaustive references

[Generalized Additive Models in R · A Free Interactive Course](#)

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Mundo AI, Tipton JR, Muldoon TJ. Generalized additive models to analyze nonlinear trends in biomedical longitudinal data using R: Beyond repeated measures ANOVA and linear mixed models. *Stat Med*. 2022;41(21):4266-4283. doi:10.1002/sim.9505

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Thank you for your attention!

Let's stay connected: odile.coudert.berthion@ipsen.com