Translational Modelling of Vemurafenib, Selumetinib and Docetaxel in Metastatic Melanoma with Virtual Tumour Clinical

PHYSIOMICS
rational therapeutics

The Need for a Virtual Tumour: Cancer is a Multi-Scale Phenomenon

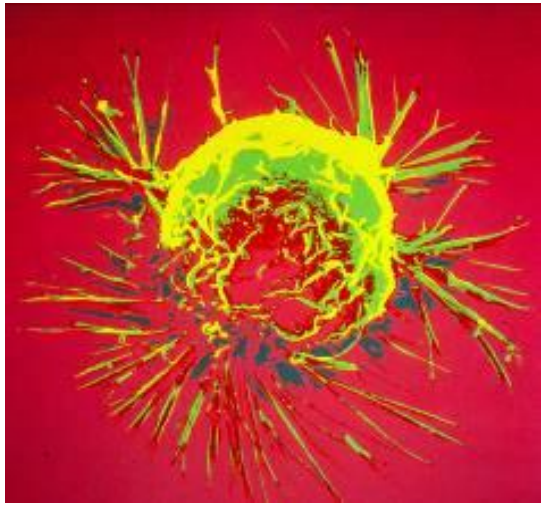


Figure A: Electron micrograph of a single breast cancer cell.
Source: National Cancer Institute.

10 - 30 µm across

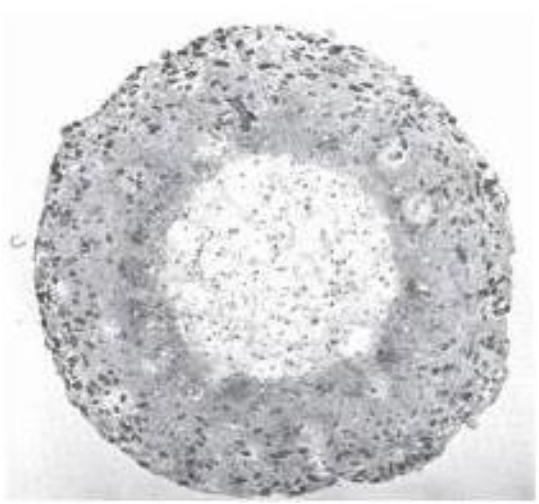


Figure B: Avascular multicellular tumour.
Source: J. Folkman, M. Hochberg, J. Exper. Medicine, 138: 745-753, 1973.

10^7 cells
1 mm across

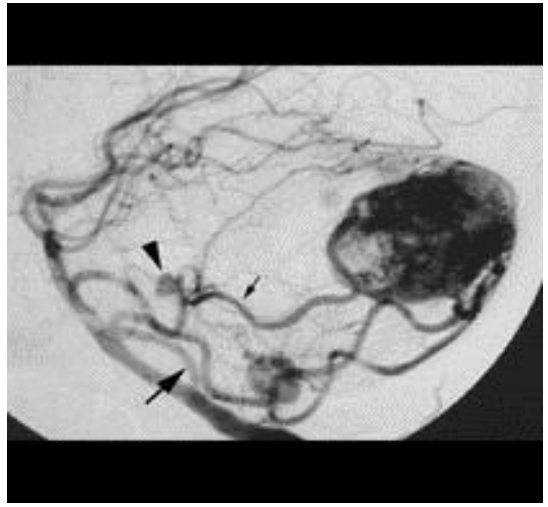


Figure C: Angiogram of a patient with a large vascular brain tumour. Arrows and arrowhead point to prominent blood vessels feeding this tumour. *Source: Standford Hospital.*

10^{11}-10^{12} cells
5-20 cm across

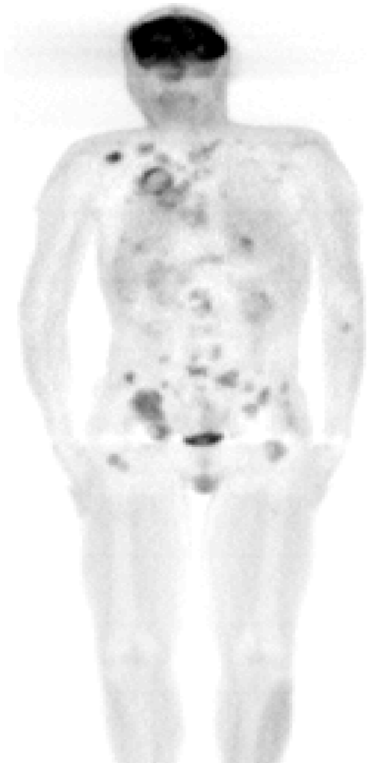


Figure D: Whole-body 18-FDG (fluorodeoxyglucose) imaging of a patient with small cell carcinoma of the lung.
Source: Unité d'Imagerie Moléculaire et de Radiothérapie Expérimentale Cliniques Universitaires Saint-Luc Bruxelles.

Cancer is a multi-scale phenomenon, hence it must be modelled on many levels

Virtual Tumour - Background

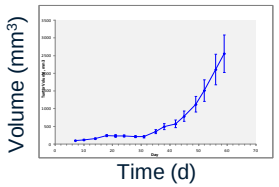
- **Physiomics' Virtual Tumour focusses on key tumour dynamics**
  - Tumour growth / spatial aspect
  - Individual cell / synchronisation
  - Predict drug effects on tumour
  - Does not try to replicate the full complexity of biological systems
- **Agent-based model, each cell (agent) contains a different instance of the model**
- **Tumours contain a heterogeneous cell population**

Virtual Tumour - Background

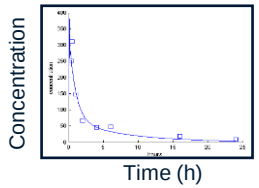
- **Preclinical**
  - Predicts the change in mean tumour volume over time
    - *Over 35 preclinical studies have confirmed the predictive capability of the model*
  - The model describes the growth of a single tumour
- **Clinical**
  - Predict the change in mean tumour diameter over time for all lesions
    - *From the preclinical work we have learnt that the mean behaviour is predictable*
- **Moving from preclinical to clinical setting and vice versa**
  - Current pharma approach involves merely matching PK between xenograft and man. We also take into consideration the different tumour growth dynamics.
  - Adjust certain key parameters we have identified as important for reflecting the different tumour growth rates between xenograft and man.

Virtual Tumour Preclinical Mechanics

1) Cell line growth data: control xenograft growth curves

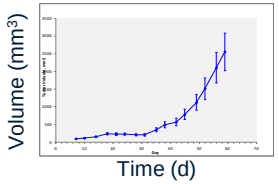


2) Compound PK data: plasma/tumour time courses

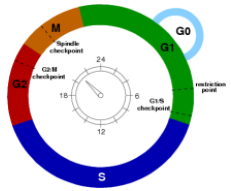


3) Compound PD data:

- xenograft inhibition data (growth curves)

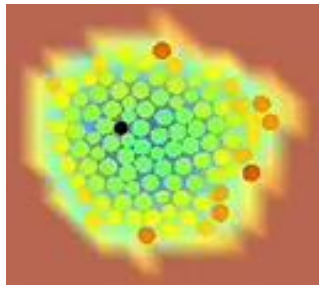


- **biomarker data** (cell cycle, cell death, target biomarkers)



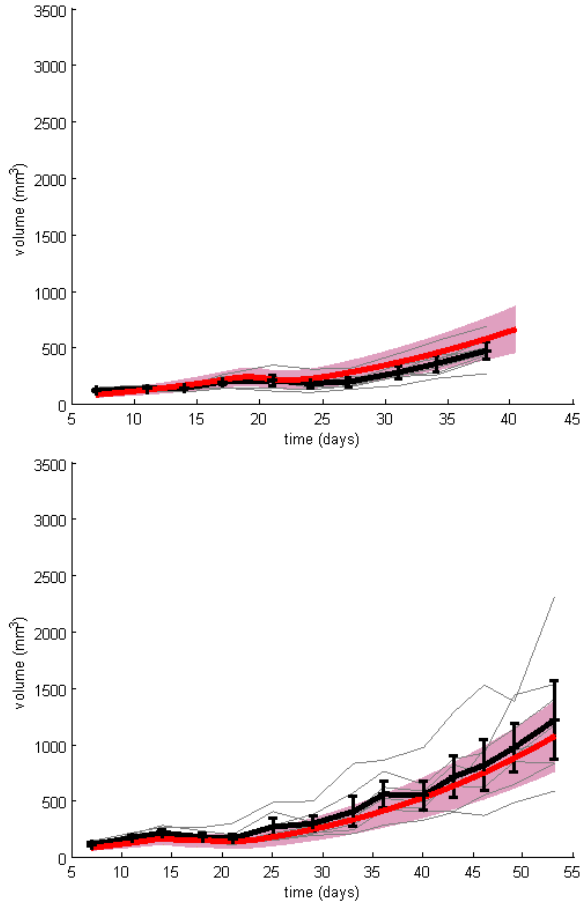
Required data
Optional data

Virtual Tumour



proprietary cell population model

Tumour growth inhibition for selected schedules

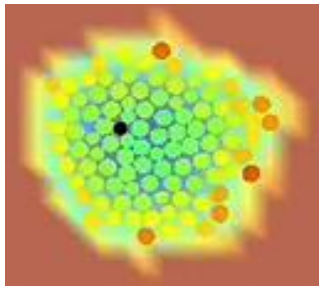


Prediction
Mean → Confidence interval

Experiment
Individual mice
Mean and standard error

Virtual Tumour Clinical
Model Development

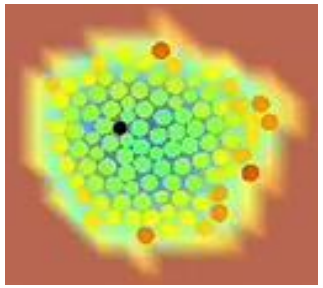
Preclinical Virtual Tumour



proprietary cell population model

- **Literature Data across numerous tumour types**
  - Growth and decay rates of clinical tumours.
  - Variability in durations of cell-cycle phases.
- **Key patient data**
  - Human PK for drug of interest. Usually from a phase I study.
  - How quickly a lesion shrinks. From clinical trials on other drugs in the same indication.

Virtual Tumour Clinical



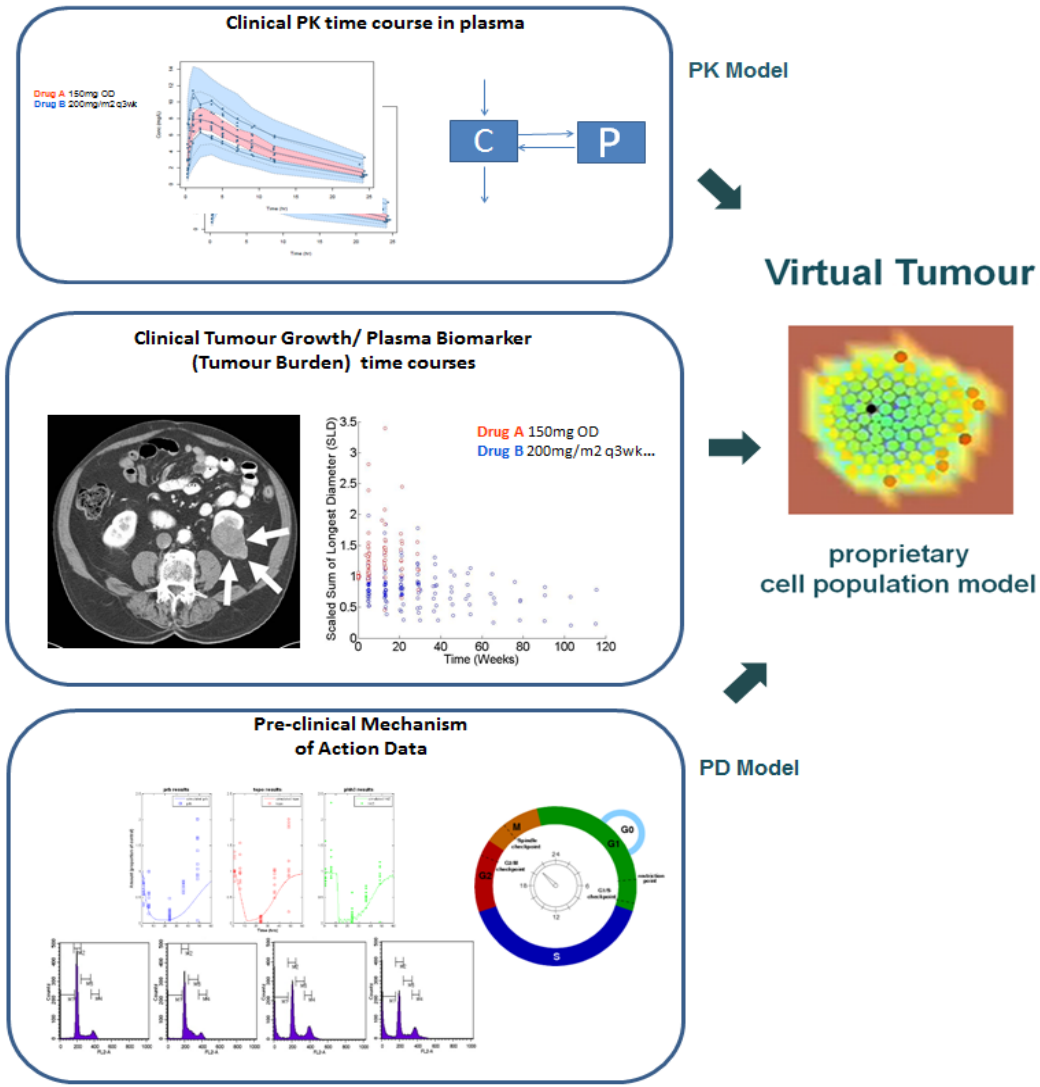
proprietary cell population model

Virtual Tumour Clinical Development

- Biomedical Catalyst funding award from the UK Technology Strategy Board (July 2013- March 2014)

Technology Strategy Board
Driving Innovation

- NIH collaboration within metastatic castrate-resistant prostate cancer
- Oxford University clinical centre to look at three cancer types
- Advanced discussion with large pharma to provide large clinical data sets
- Early results suggest that the existing preclinical model architecture may be appropriate for making clinical predictions
- Large unmet need – interest from almost every potential partner



Clinical to Preclinical (Back Translation)
Metastatic Melanoma

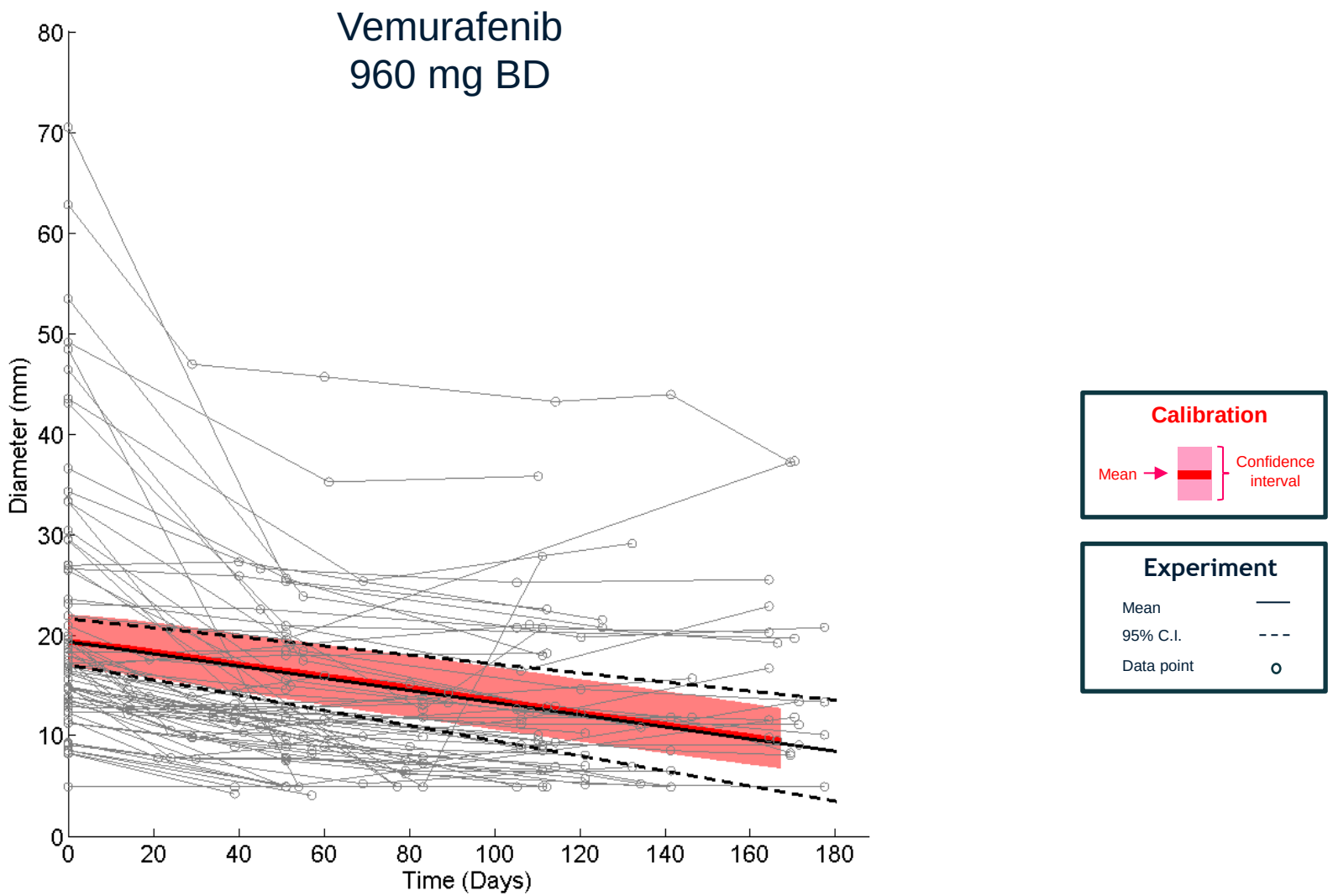
Vemurafenib

- **Clinical data**
  - 20 patients where each lesion was monitored over time
  - Total number of evaluable lesions: 69
  - FDA report contains a PK model
- **Preclinical data**
  - COLO 205 xenograft (colorectal cell line with BRAF V600 mutation) for which we have change in tumour volume for different doses of the drug
  - Literature PK model
- **Mechanism of action**
  - B-Raf inhibitor
  - Drug is known to exert its anti-tumour effect through causing G1 arrest

Modelling Plan

- **Step 1:** Analyse clinical data using population analysis approach
- **Step 2:** Calibrate Virtual Tumour to the mean clinical signal
  - Clinical PK model sourced from literature
- **Step 3:** Switch clinical growth settings for preclinical growth settings and calibrate preclinical model to control growth
- **Step 4:** Predict preclinical monotherapy effects
  - Preclinical PK model sourced from literature
- **Step 5:** Compare prediction with actual results

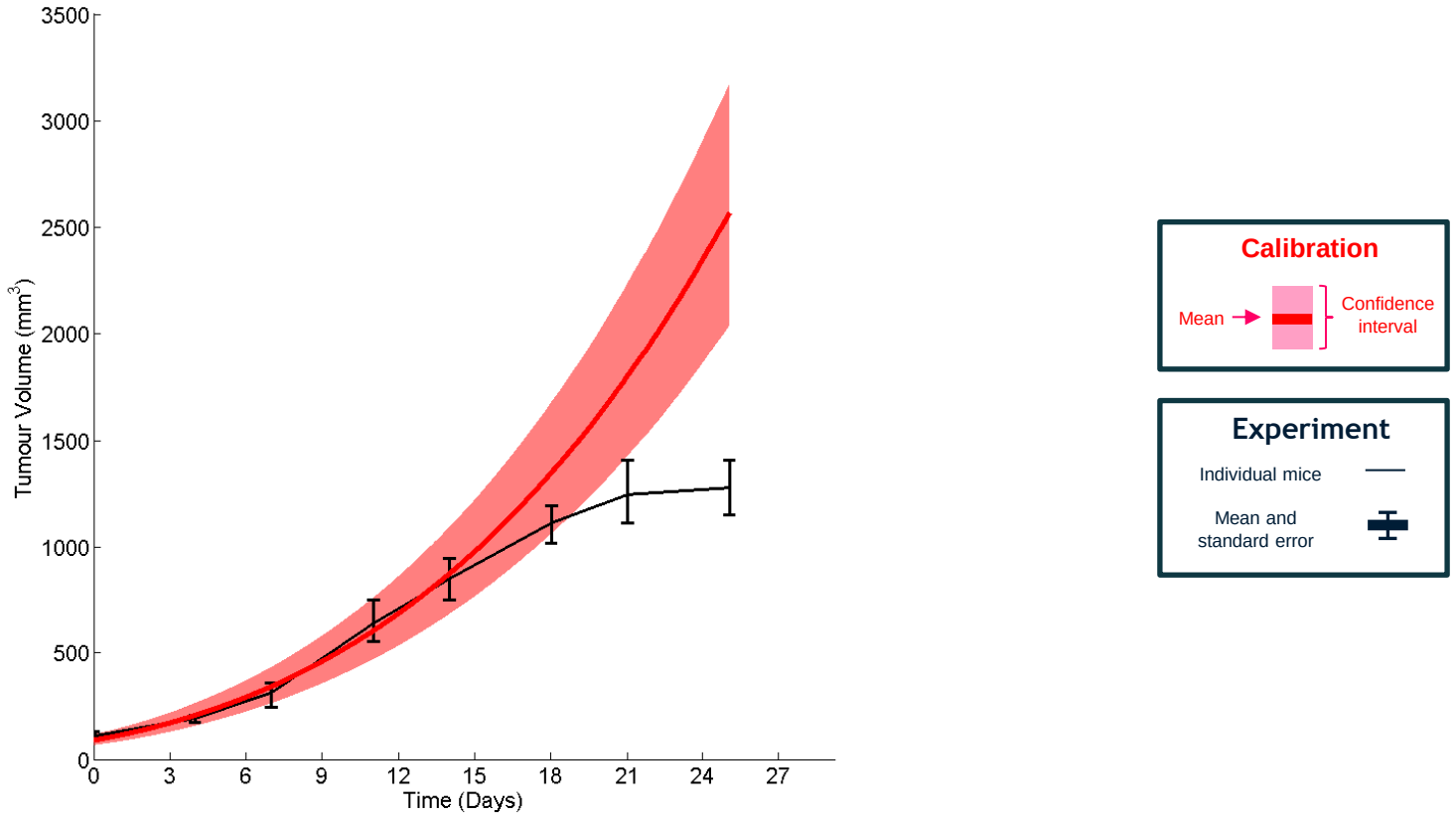
Steps 1 and 2: Clinical Calibration



Evolutionary dynamics of cancer in response to targeted combination therapy. eLife. DOI: 10.7554/eLife.00747.001.

Step 3: Preclinical Control Calibration

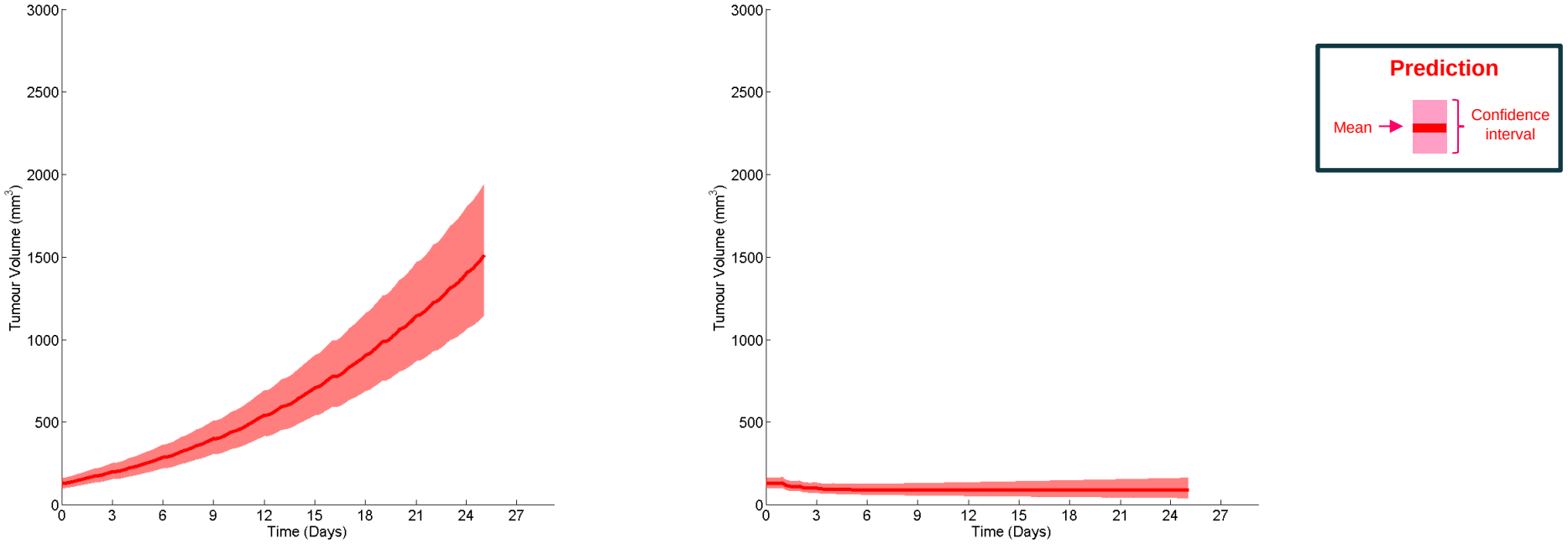
- **Mouse drop-outs affect the mean behaviour at late time points**
  - Focus on early dynamics as mice are usually sacrificed once tumour volumes reach a certain size



Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010. 467(7315): 596-599.

Steps 4 and 5: Preclinical Prediction

- **Monotherapy predictions compare well with experimental observations**
  - Left panel 6 mg/kg QD, right panel 20 mg/kg QD



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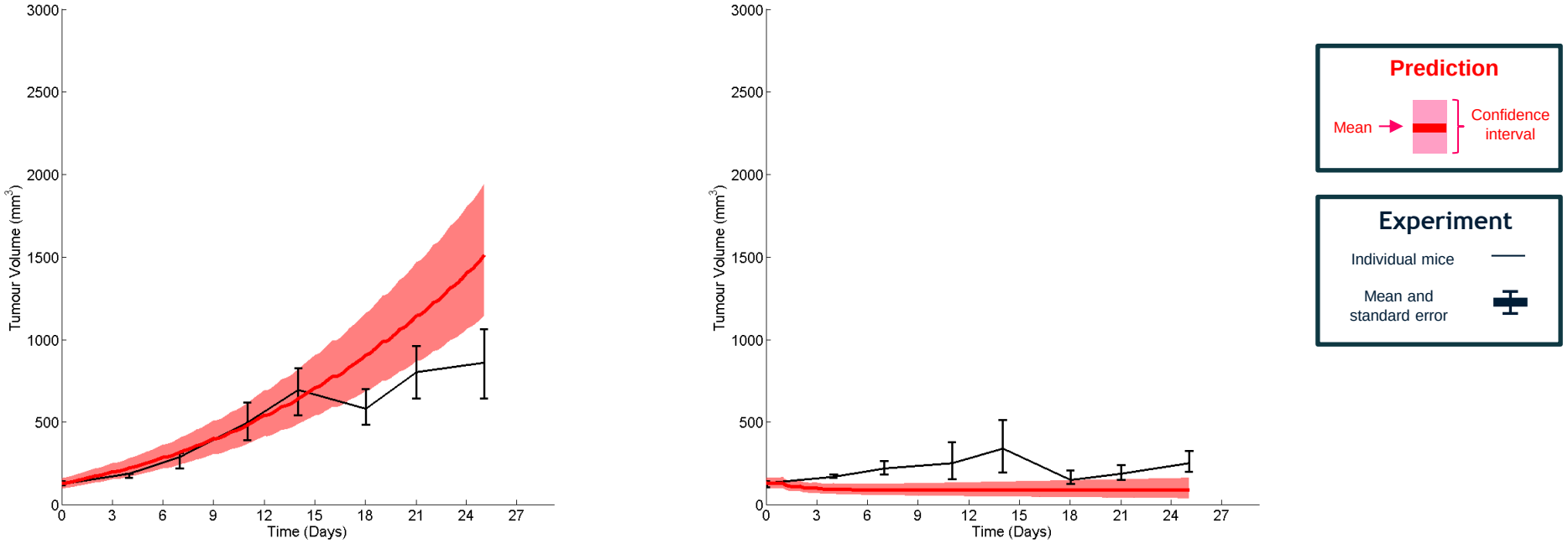
Steps 4 and 5: Preclinical Prediction

- **Monotherapy predictions compare well with experimental observations**
  - Left panel 6 mg/kg QD, right panel 20 mg/kg QD
- **This was a colorectal cancer xenograft (COLO 205) which had BRAF V600 mutation**
  - Mutational background more important than tissue type? See later



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Summary

- **Calibrated Virtual Tumour to monotherapy changes in individual clinical lesions**
- **Model prediction:**
  - Captured the preclinical dynamics very well
- **Successful back-translational validation**
  - Predicted the effects reasonably well

We shall now look at a forward translational project in this disease area...

Preclinical to Clinical
Metastatic Melanoma

PHYSIOMICS
rational therapeutics

Case Study – Translational Qualification
Predicting Clinical Efficacy Using Preclinical Data

ADVANCE:	Qualification of the translational capability of the Virtual Tumour
OBJECTIVE:	To determine whether our technology could accurately predict the mean change in tumour size over time in a phase II clinical study of docetaxel vs. docetaxel/selumetinib in BRAF WT metastatic melanoma
PARTNER:	Mark Middleton, Oxford ECMC
START POINT:	Single drug xenograft dose-response data, preclinical and clinical PK
DURATION:	6 weeks
OUTCOMES:	Correctly predicted mean change in tumour size over time in both arms of the study and provided schedule options to ameliorate toxicities

Docetaxel/Selumetinib

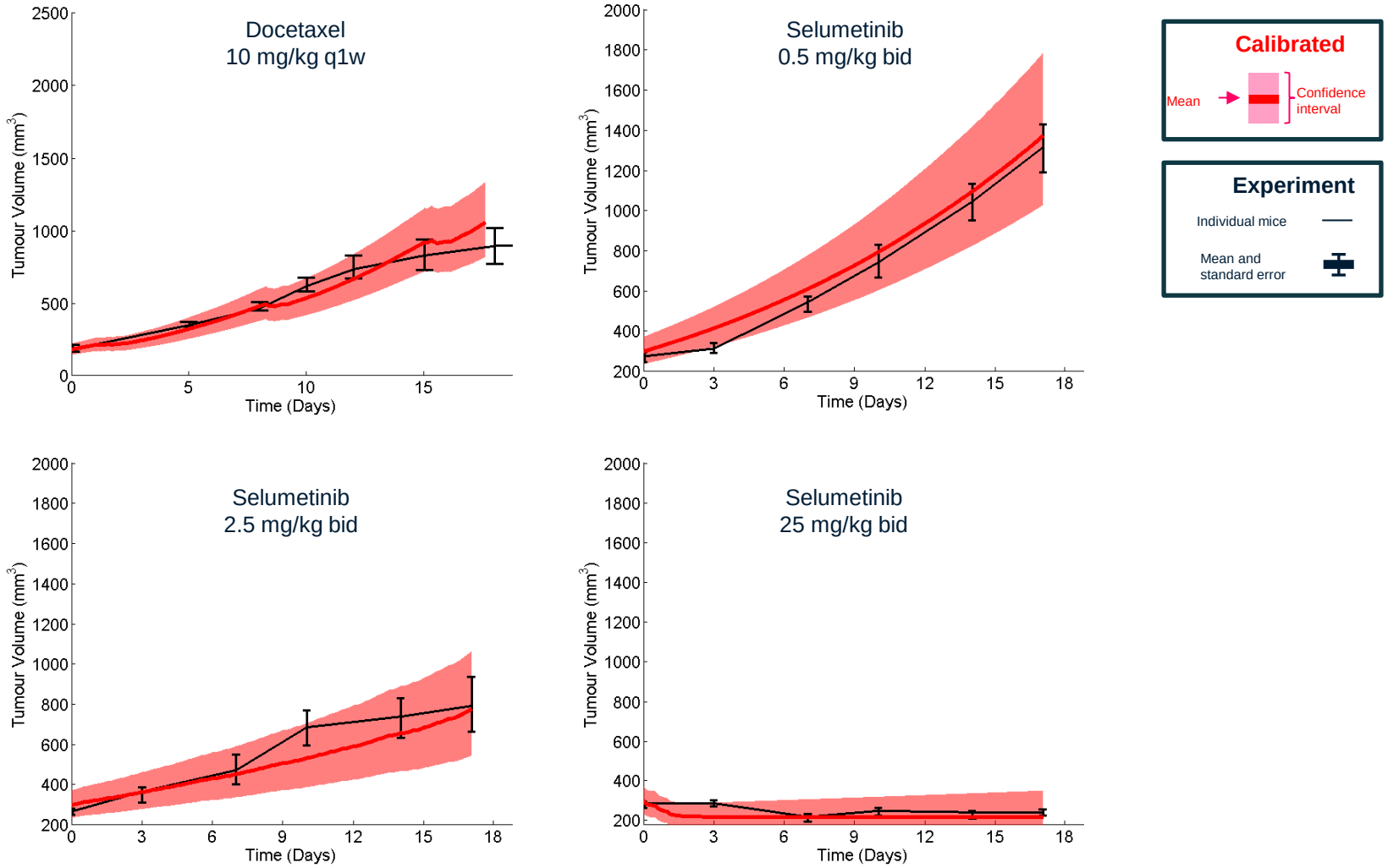
- **AstraZeneca sponsored randomised phase II study: docetaxel/selumetinib v docetaxel**
  - 40 patients in each arm
  - ~100 lesions in each arm
  - BRAF WT setting
- **Selumetinib is a MEK inhibitor being investigated in numerous disease areas**
  - Phase III combination with docetaxel currently ongoing in NSCLC
- **Trametinib (GSK) MEK inhibitor was approved last year in the BRAF MUT setting**
- **Literature search was required for:**
  - Preclinical xenograft and PK
  - Clinical PK

Modelling Plan

- **Step 1:** Calibrate Virtual Tumour to preclinical data for each agent
  - Literature PK and xenograft data sourced from literature
- **Step 2:** Switch preclinical growth settings for clinical growth settings
- **Step 3:** Predict the two-arm phase II trial
  - Clinical PK models sourced from literature
- **Step 4:** Population analysis of the clinical study
- **Step 5:** Compare prediction with actual result

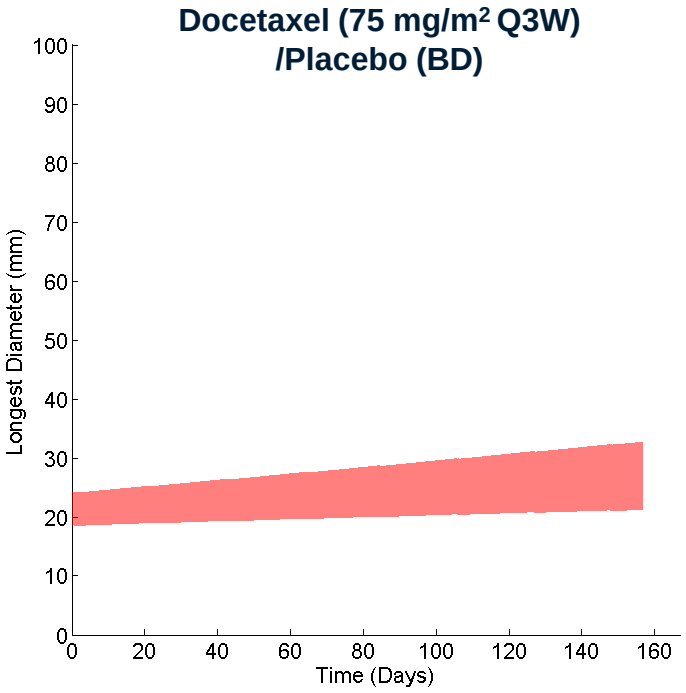
Case Study – Translational Validation
Step 1: Preclinical Calibration

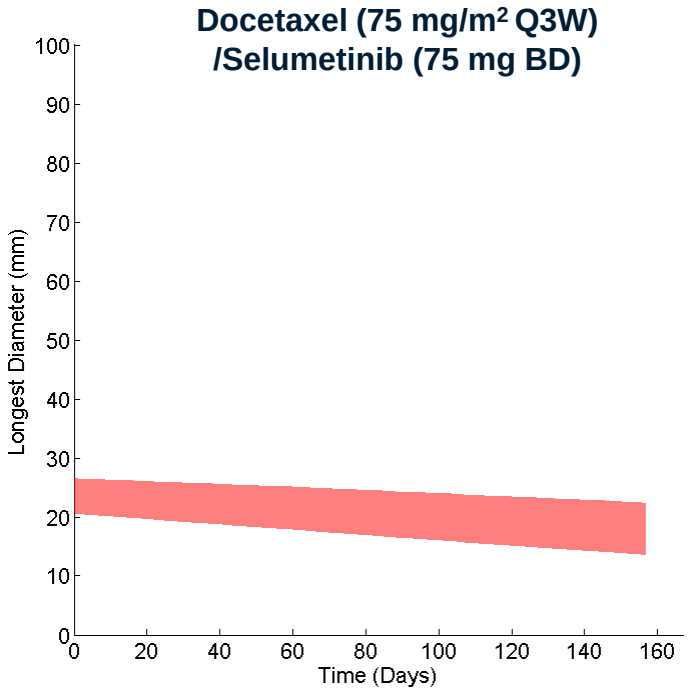
➡ **Calibration of the Virtual Tumour to preclinical monotherapy data**

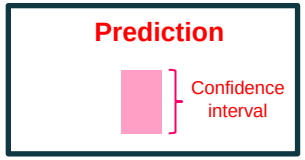


Case Study: Translational Qualification
Steps 2 and 3: Prediction

- **Replace preclinical growth settings with clinical growth settings**
  - Baseline longest diameters are provided as initial inputs
- **Replace preclinical PK with clinical PK and simulate predictions**

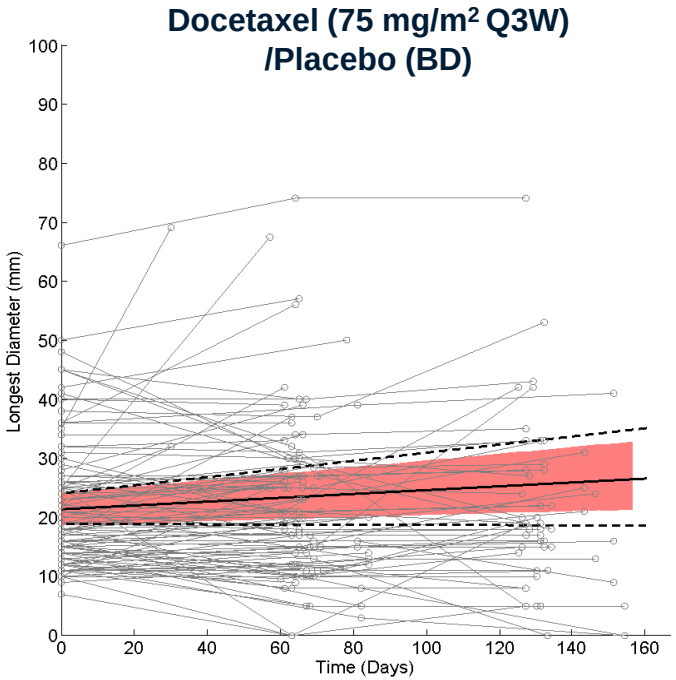


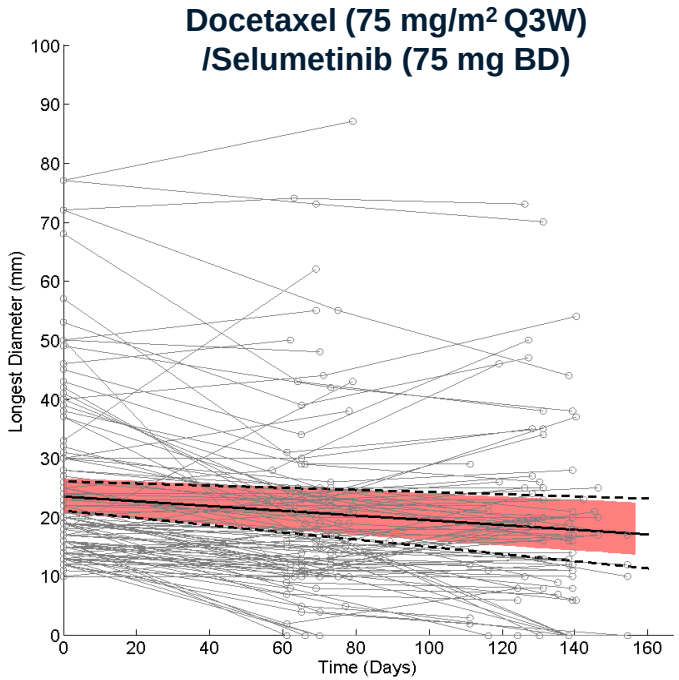




Case Study: Translational Qualification
Steps 4 and 5: Qualification

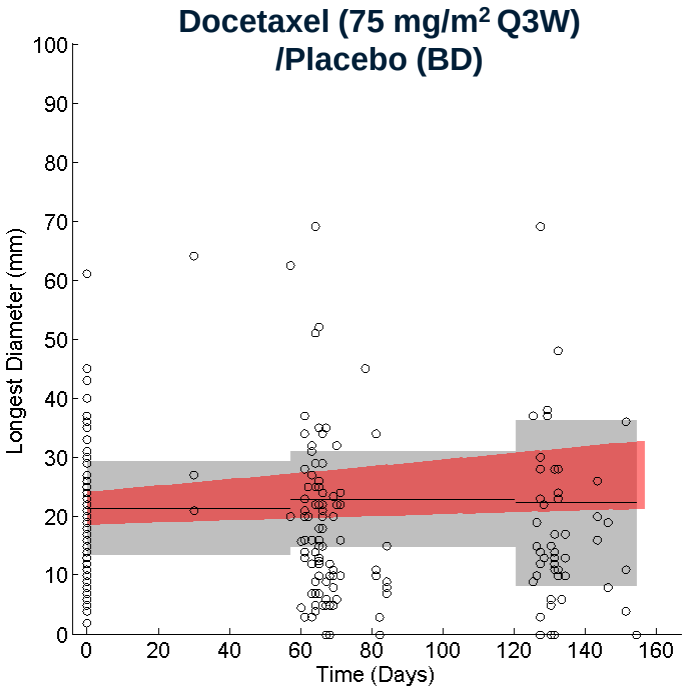
- **Perform a population analysis of the clinical data and overlay the results**
- **Accurate predictions for both arms of the study**
  - Final Study Result: overall response rate (ORR) 32% Doc/Mek v 14% Doc (p = 0.059)

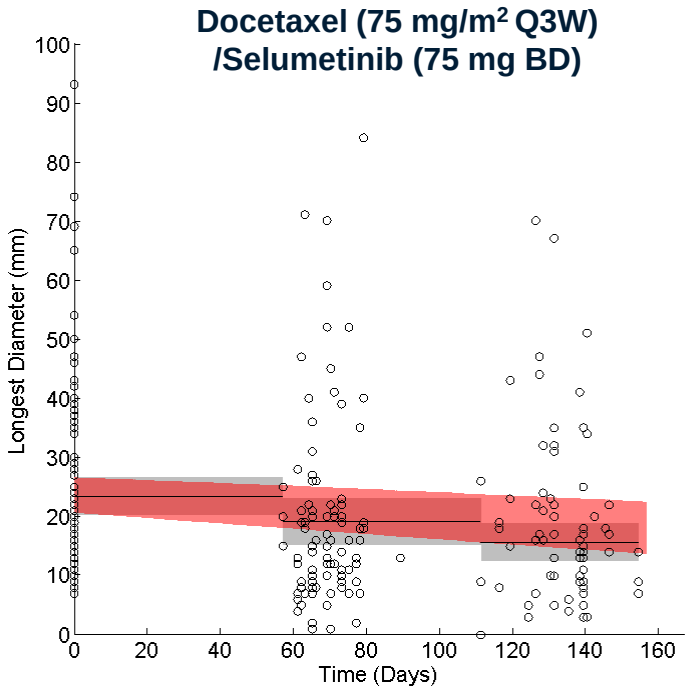


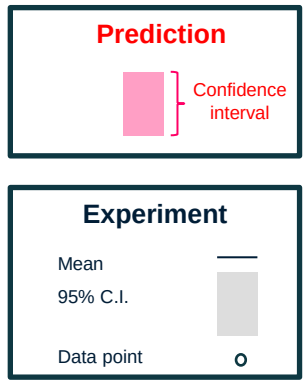


Case Study: Translational Qualification
Steps 4 and 5: Qualification

- **Biostatistics view: bin the data according to three groups and calculate the mean and 95% confidence interval**
- **Accurate predictions for both arms of the study**
  - Final Study Result: overall response rate (ORR) 32% Doc/Mek v 14% Doc (p = 0.059)



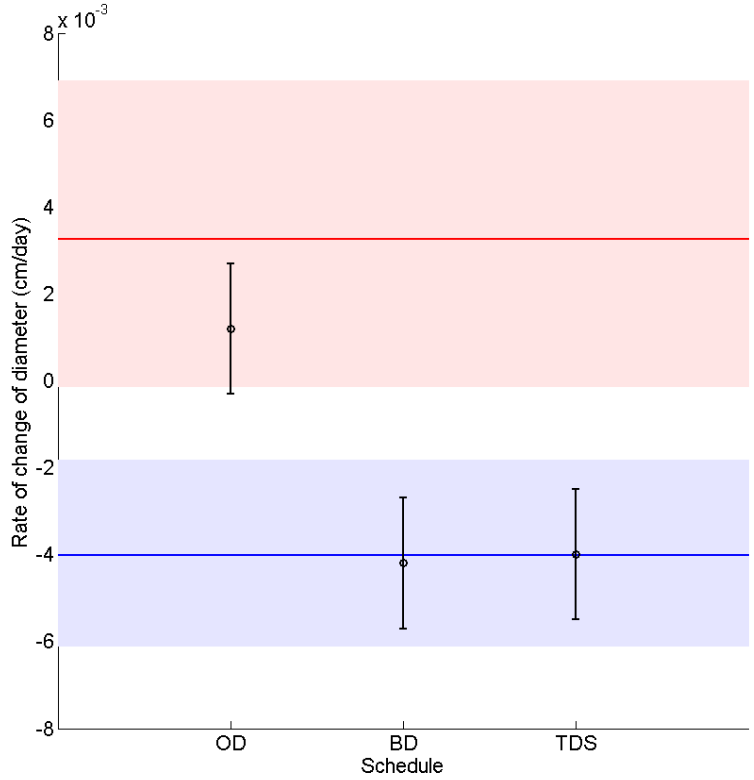




Summary

- **Successfully predicted the results of the 2-arm clinical phase 2 trial using monotherapy preclinical efficacy data**
  - Performed further predictions for Oxford's ECMC to look at different regimens e.g.

- **What happens if we alter the way Selumetinib is given in a day?**
  - Legend:
    - *Docetaxel (75 mg/m^2) mean (red) and 95% C.I. (pink region)*
    - *Docetaxel (75 mg/m^2)/Mek (75 mg BD) mean (blue) and 95% C.I. (light blue region)*
    - *Model predictions open circles and C.I.*
    - *Total daily dose is 150 mg*
- **No difference between BD and TDS for the same total daily dose.**



Conclusion

- **Successfully predicted the mean change in lesion size for each arm of the phase II trial, using monotherapy preclinical efficacy data and clinical PK data**
  - Performed further predictions for Oxford ECMC, exploring different dosing regimens and changing docetaxel for paclitaxel
- **Virtual Tumour Clinical can provide significant cost-savings**
  - accurate translation of preclinical efficacy reduces the number of clinical studies required to find optimal doses and schedules
- **Virtual Tumour Clinical could reduce attrition rates**
  - Optimized regimens can enhance efficacy, increasing the chance of clinical trial success

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