

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

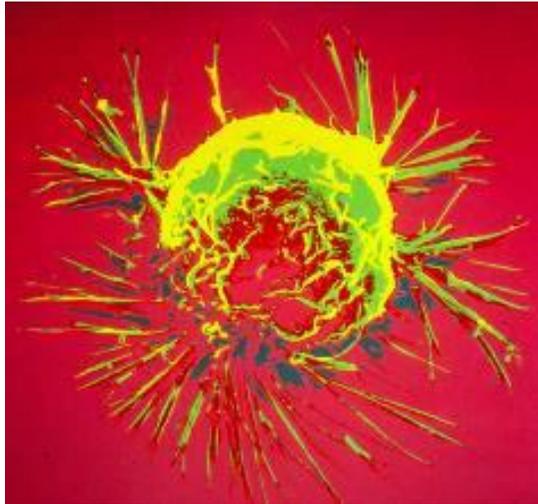


Figure A: Electron micrograph of a single breast cancer cell.
Source: National Cancer Institute.

10 - 30 μm across

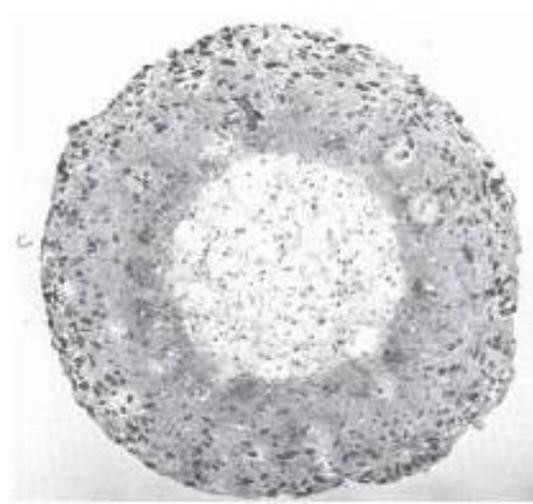


Figure B: Avascular multicellular tumour.
Source: J. Folkman, M. Hochberg, *J. Exper. Medicine*, 138: 745-753, 1973.

**10^7 cells
1 mm across**

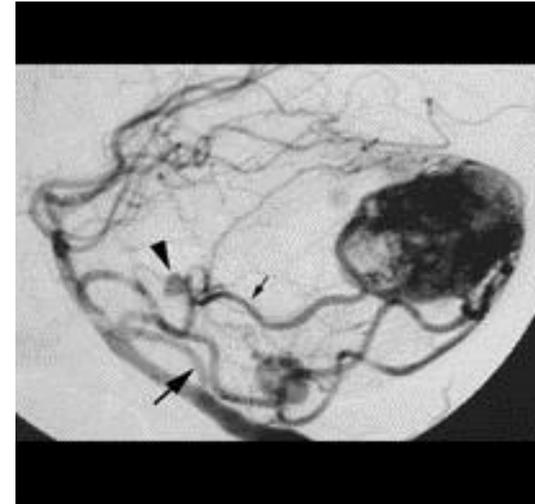


Figure C: Angiogram of a patient with a large vascular brain tumour. Arrows and arrowhead point to prominent blood vessels feeding this tumour. Source: Stanford Hospital.

**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*

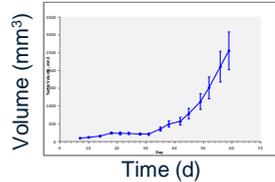
➔ Moving from preclinical to clinical setting and vice versa

- ➔ 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.

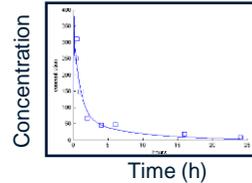


Virtual Tumour Preclinical Mechanics

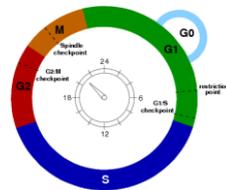
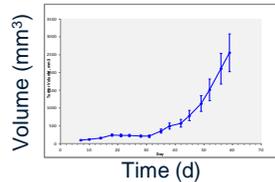
1) Cell line growth data: control xenograft growth curves



2) Compound PK data: plasma/tumour time courses



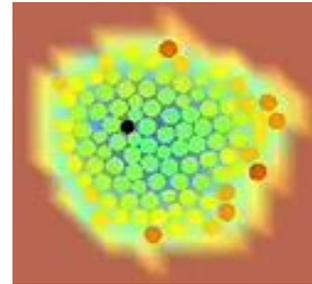
3) Compound PD data:
- xenograft inhibition data (growth curves)
- biomarker data (cell cycle, cell death, target biomarkers)



Required data
Optional data

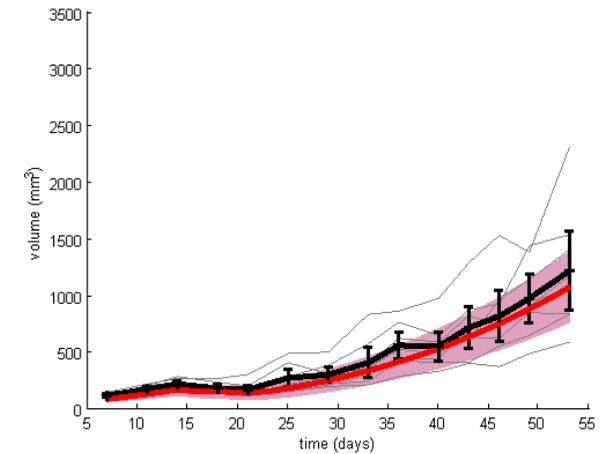
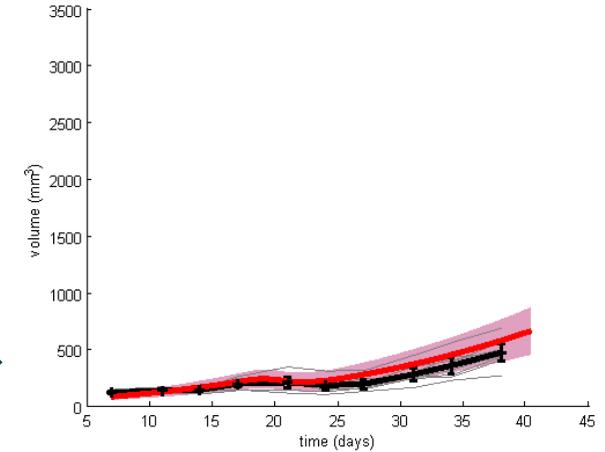


Virtual Tumour



proprietary cell population model

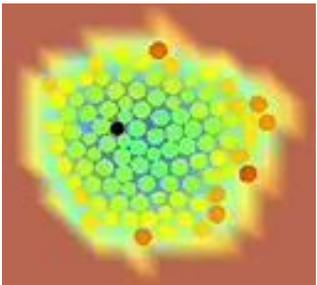
Tumour growth inhibition for selected schedules



Prediction		Experiment	
Mean →	Confidence interval	Individual mice	Mean and standard error



Preclinical Virtual Tumour



proprietary cell population model



➔ Literature Data across numerous tumour types

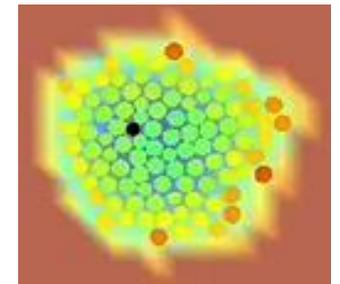
- ➔ Growth and decay rates of clinical tumours.
- ➔ Variability in durations of cell-cycle phases.

➔ 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

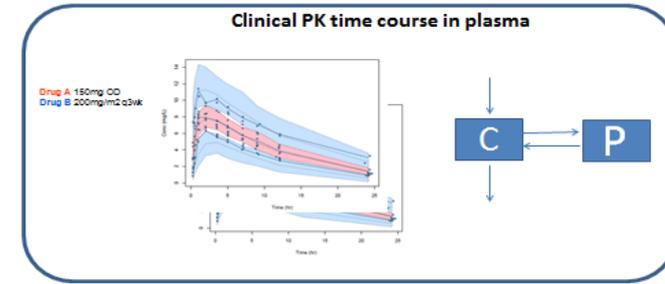


Virtual Tumour Clinical Development

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

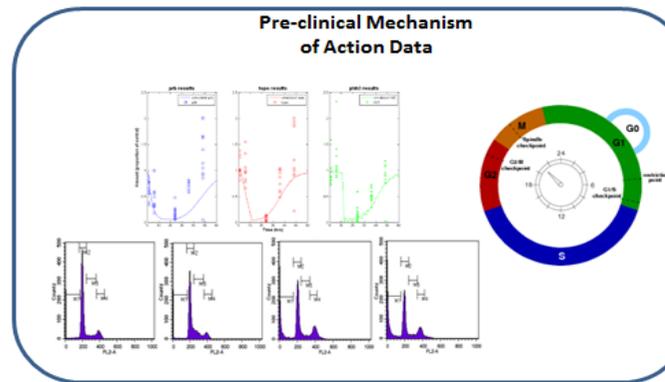
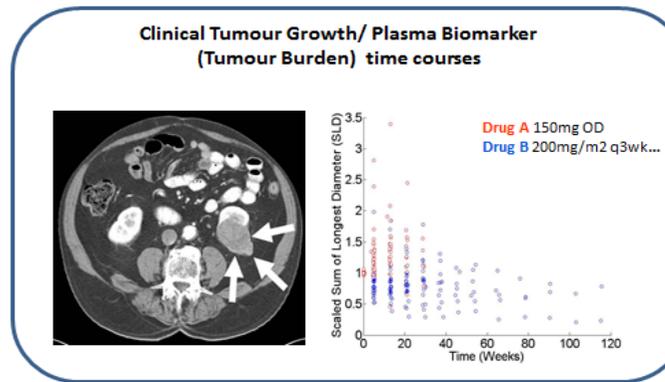


- ➔ NIH collaboration within metastatic castrate-resistant prostate cancer
- ➔ Oxford University clinical centre to look at three cancer types
- ➔ Advanced discussion with large pharma to provide large clinical data sets
- ➔ Early results suggest that the existing preclinical model architecture may be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



PK Model

Virtual Tumour



PD Model

Clinical to Preclinical (Back Translation) Metastatic Melanoma





➔ 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

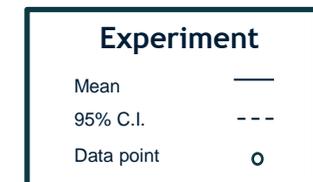
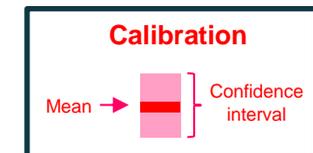
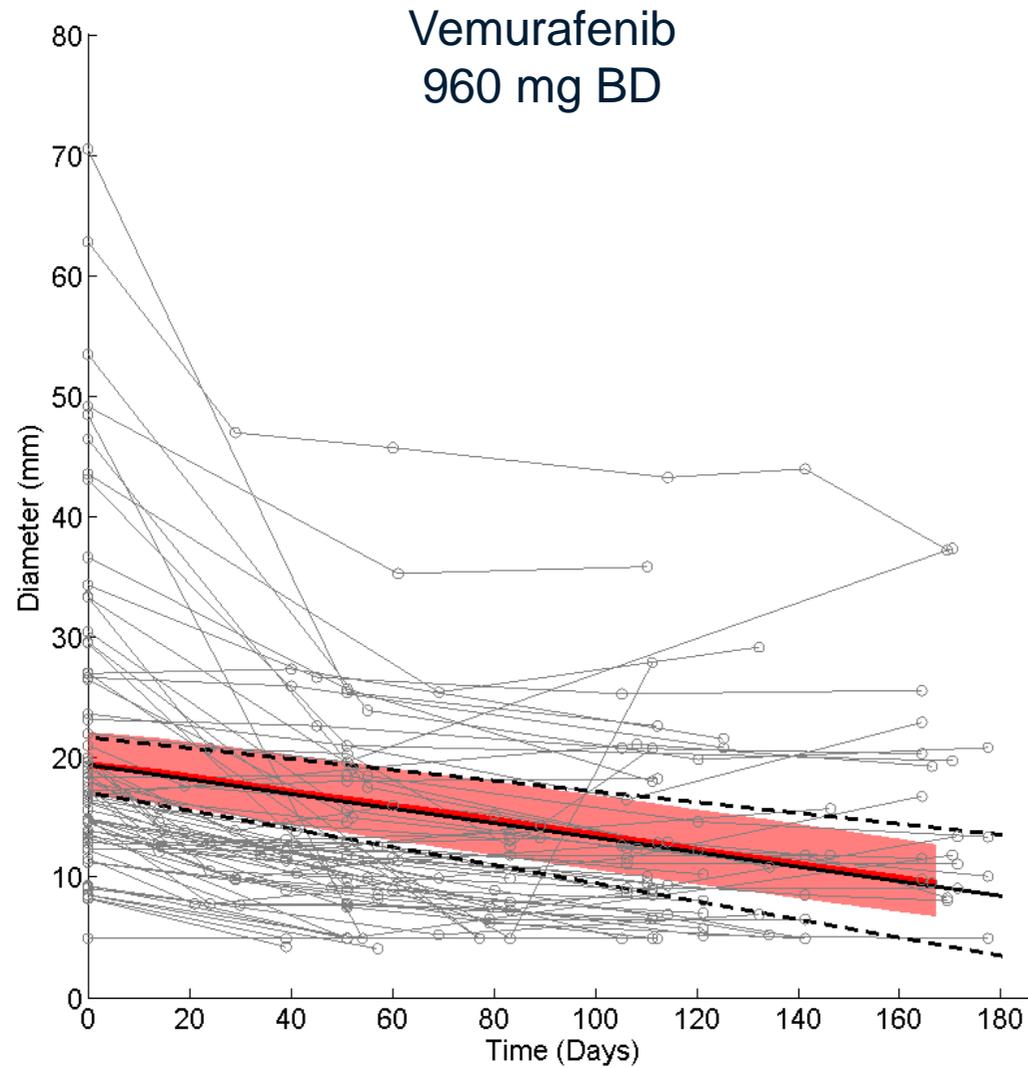
- ➔ B-Raf inhibitor
- ➔ Drug is known to exert its anti-tumour effect through causing G1 arrest



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



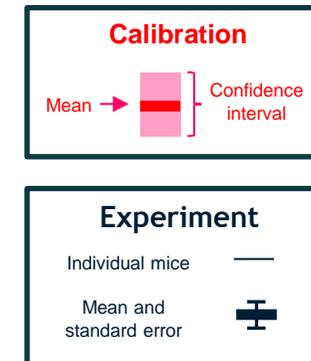
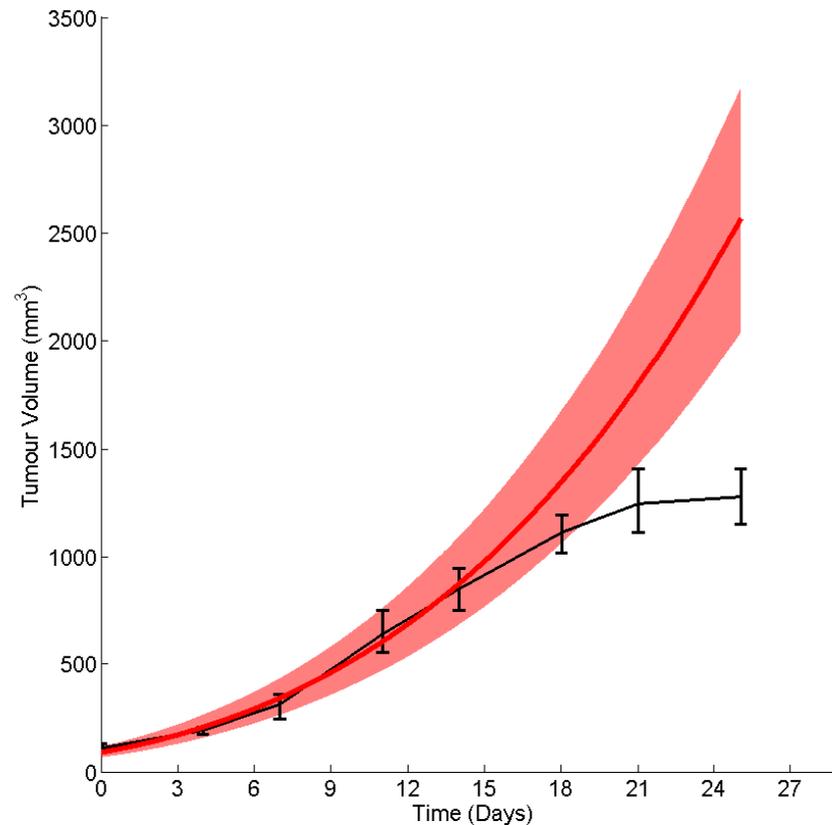
Evolutionary dynamics of cancer in response to targeted combination therapy. eLife. DOI: 10.7554/eLife.00747.001.



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



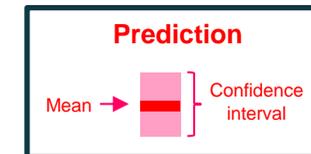
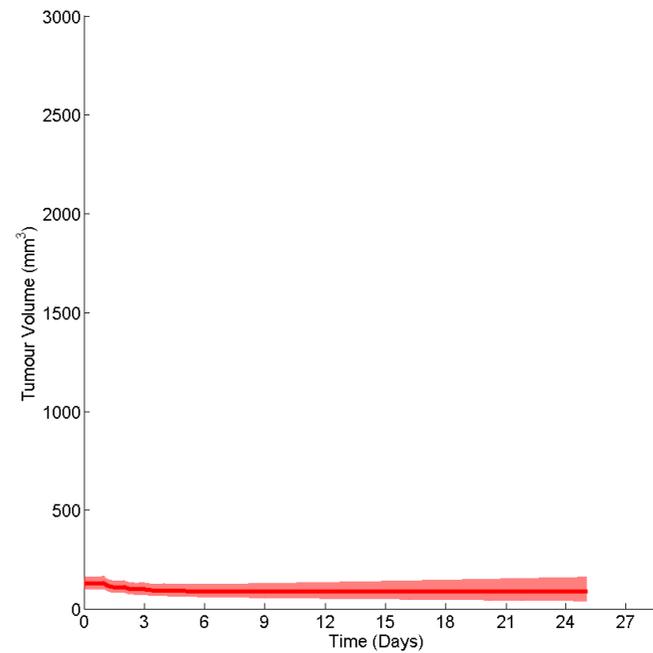
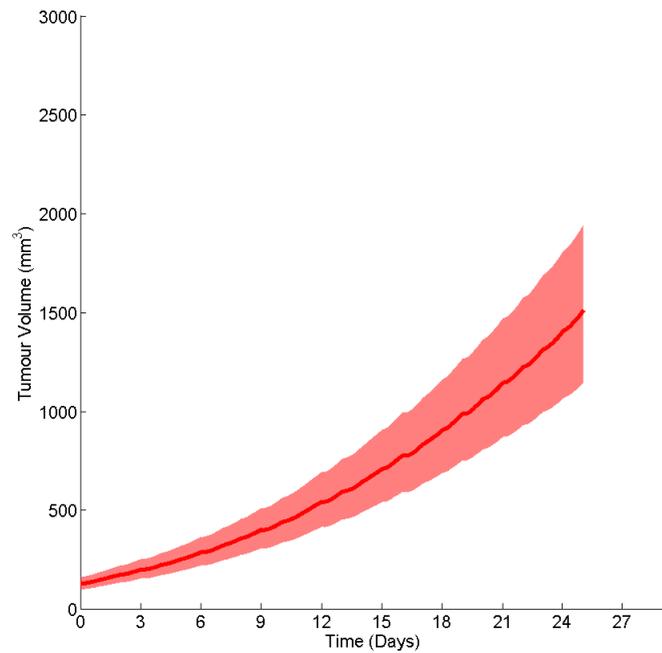
Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010. 467(7315): 596-599.



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

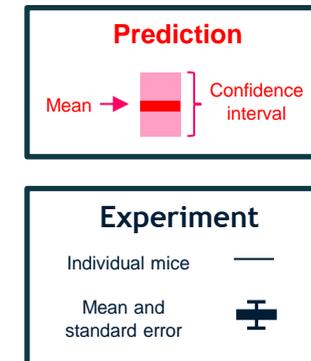
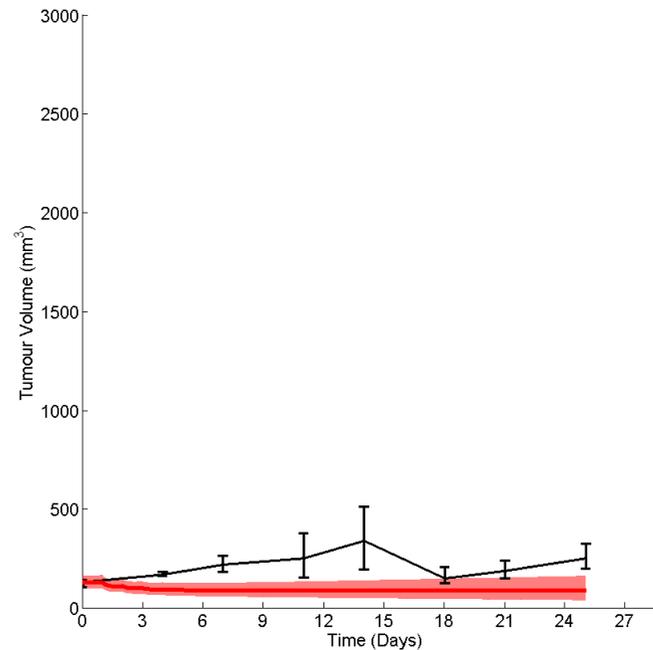
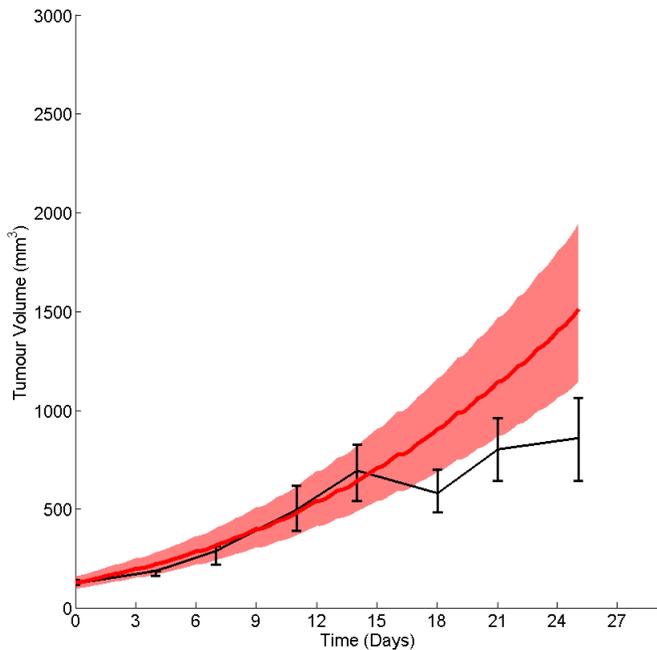


Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010. 467(7315): 596-599.



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
- ➔ **This was a colorectal cancer xenograft (COLO 205) which had BRAF V600 mutation**
 - ➔ Mutational background more important than tissue type? See later



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



- ➔ **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

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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



- ➔ **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

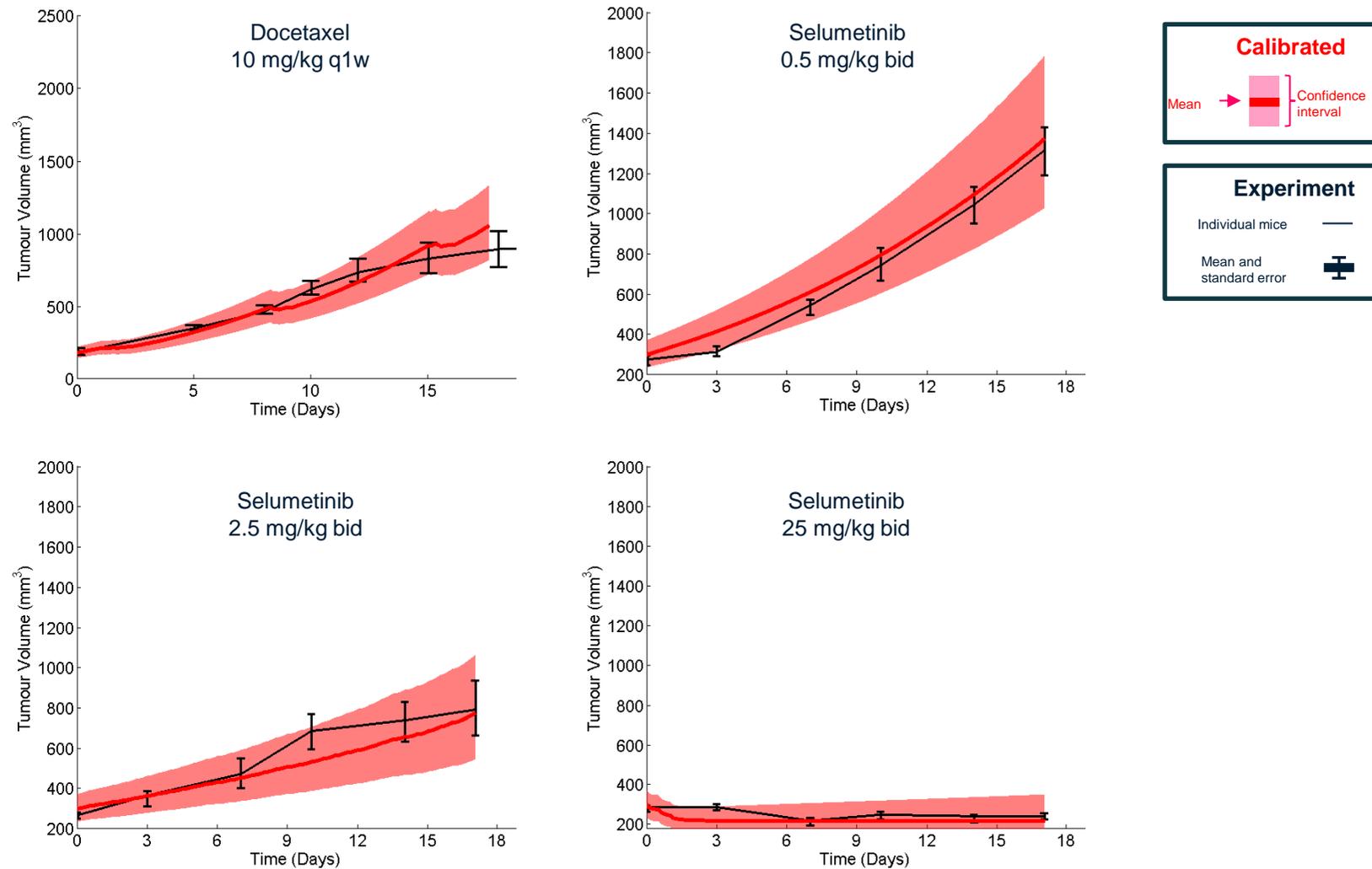
- ➔ **Step 1: Calibrate** Virtual Tumour to preclinical data for each agent
 - ➔ Literature PK and xenograft data sourced from literature
- ➔ **Step 2:** Switch preclinical growth settings for clinical growth settings
- ➔ **Step 3: Predict** the two-arm phase II trial
 - ➔ Clinical PK models sourced 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

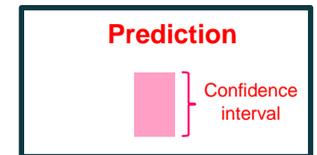
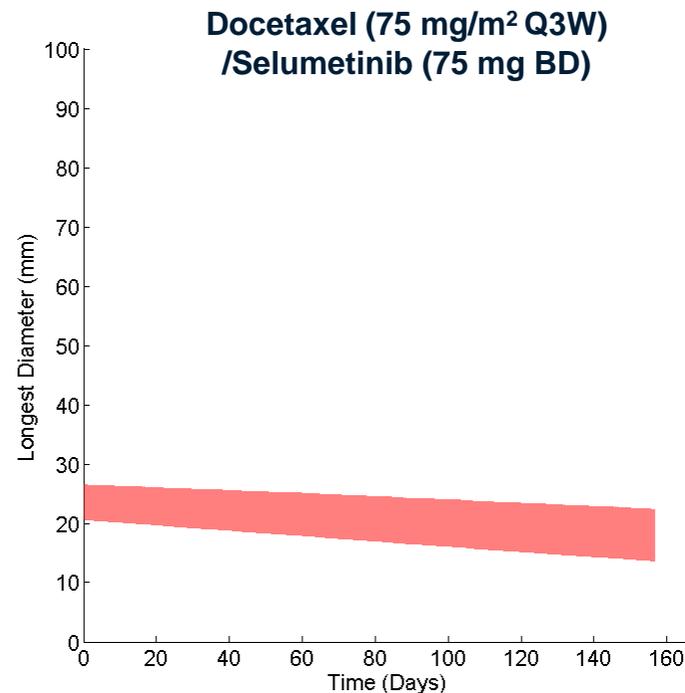
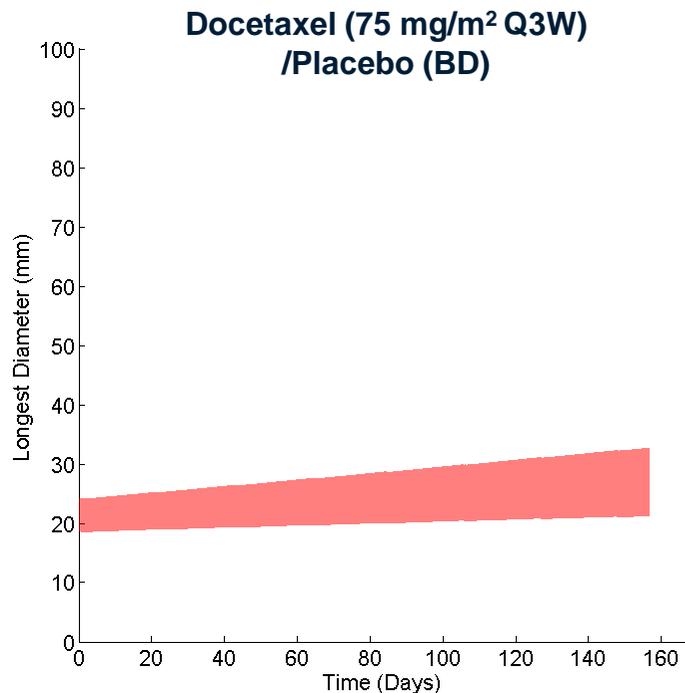


Case Study: Translational Qualification

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**

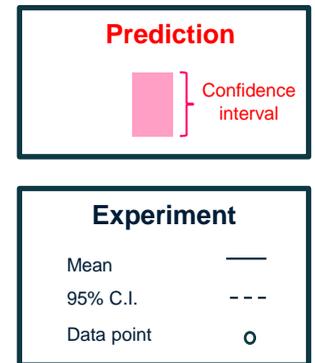
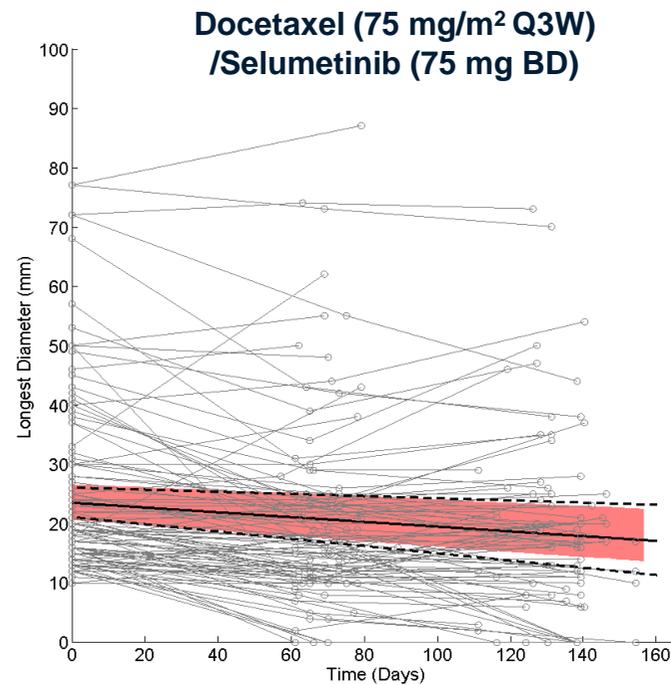
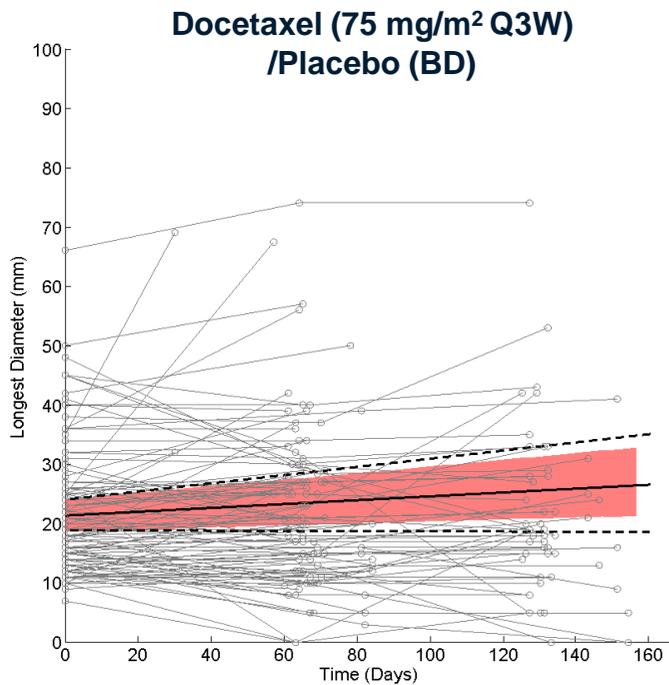


Case Study: Translational Qualification

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 ($p = 0.059$)

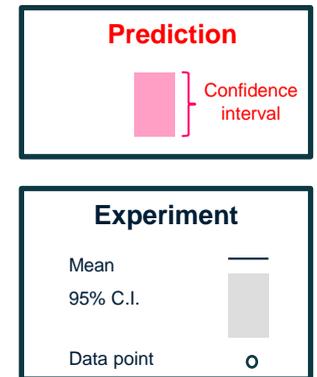
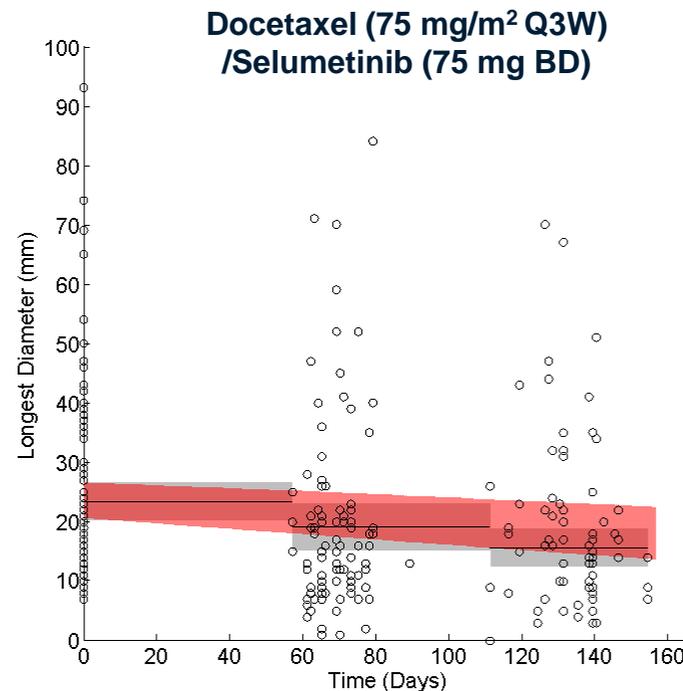
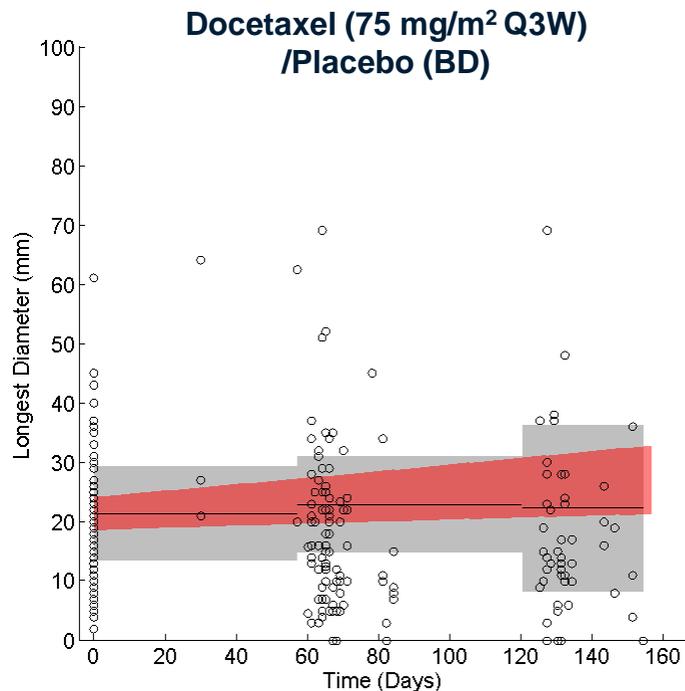


Case Study: Translational Qualification

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 ($p = 0.059$)





➔ **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:

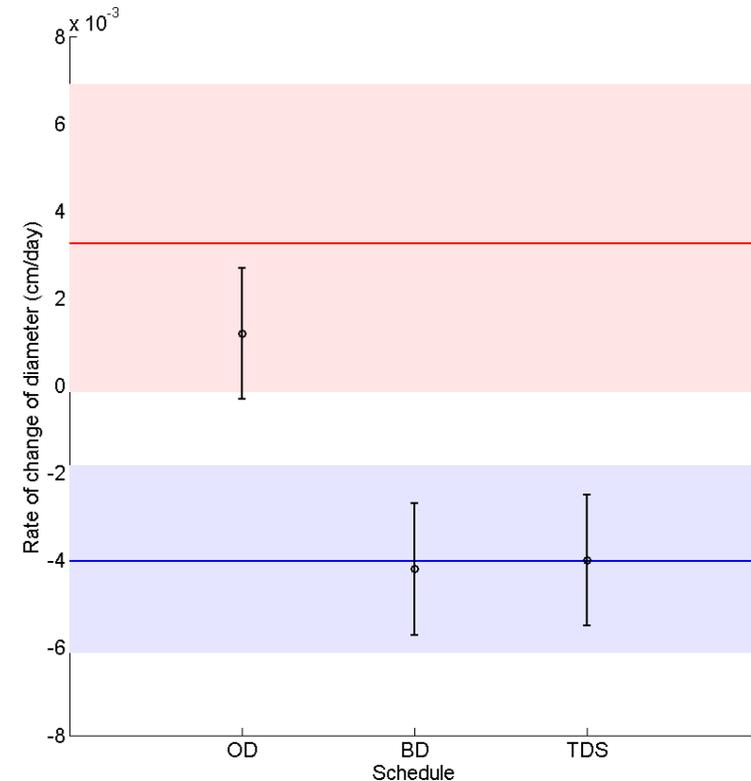
➔ *Docetaxel (75 mg/m²) mean (red) and 95% C.I. (pink region)*

➔ *Docetaxel (75 mg/m²)/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.**





- ➔ **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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