PK/PD Efficacy Modelling of Combinations to Guide Scheduling and Sequencing

Sonya Tate, PhD

Lilly | ONCOLOGY

Outline of the Presentation

- Introduction
  - Why are combination treatments so important in oncology?
  - How do we choose which drugs should be combined?
  - How do we evaluate and optimise dose/schedule combination?

- Application of semi-mechanistic PK/PD modelling (Tate et al 2016)
  - Combination of abemaciclib and vemurafenib to combat drug-induced resistance to BRAF inhibition in BRAF-mutated melanoma

- Conclusions/thoughts
  - What are the pros/cons of semi-mechanistic combination PK/PD models?
  - How routinely are such models developed/implemented in drug development?
  - Is it possible to test drug combinations in PK/PD models a priori?

Combinations in Oncology

- Combination treatments are commonly used in oncology
- Broadly two types:
  - Combination with standard of care, often for ethical reasons
  - Combination with anticipated superior effects over monotherapy
- Combinations may be identified through:
  - Current clinical practice (for SOC combos)
  - In vitro screening methods
  - Biological hypotheses
- Combination treatments may help to:
  - Increase the impact of pathway disruption through upstream and downstream targets
  - Prevent cell from recovery by targeting two survival pathways
  - Combat emerging resistance to treatment by anticipating biological changes in the cell

Lilly | ONCOLOGY

Dose Scheduling and Sequencing

- Combination treatments are often tested using simultaneous administration
  - Unless limited by toxicity (and/or DDI), doses and dosing frequencies often mimic those of the monotherapies
- However, is the treatment benefit optimised using simultaneous administration?
  - Could delaying one treatment by hours / days maximise efficacy?
- Is the same amount of drug required for efficacy?
  - i.e. does the exposure-response curve for each drug change when in combination?
- Treatment optimisation of multiple dosing scenarios in combinations would require many in vitro / in vivo studies
- PK/PD modelling can be used to compile the known quantitative pharmacology of the effects of monotherapy and combination treatment
  - Using model simulations, a variety of dosing scenarios can be evaluated
  - Allows the dose schedule and sequencing to be optimised without the extensive resources required for in vivo or clinical evaluations

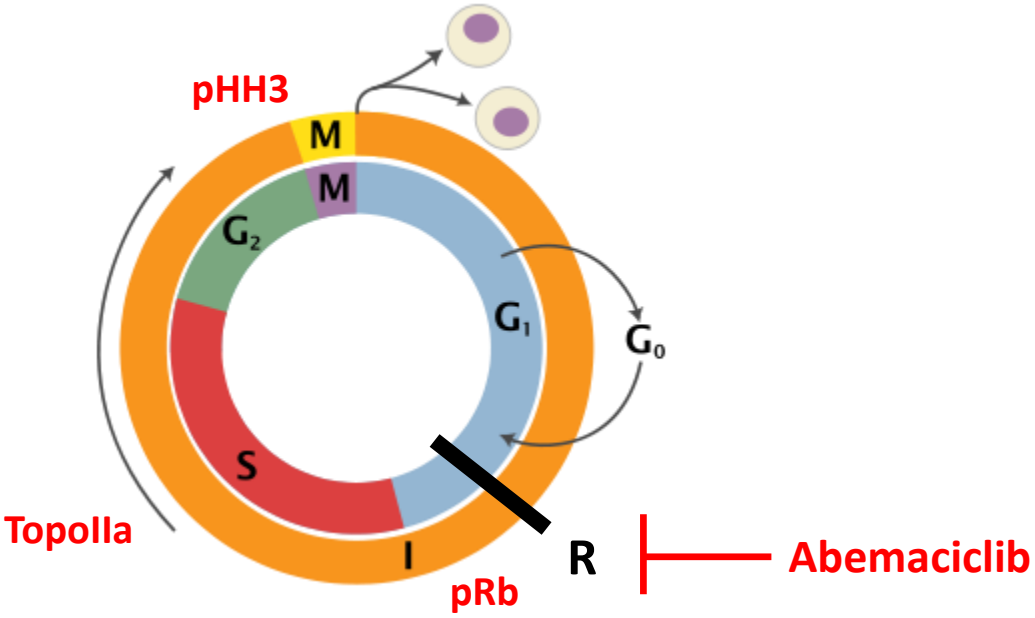
Application of Semi-Mechanistic PK/PD Modelling for Combinations in Oncology

Tate et al., 2016. BJC [accepted]

Lilly | ONCOLOGY

Abemaciclib Mechanism of Action

- Abemaciclib is a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) currently in clinical development
  - Abemaciclib-mediated inhibition of CDK4/6 induces cell cycle arrest
  - CDK4/6 inhibition is directly measured by activity of pRb

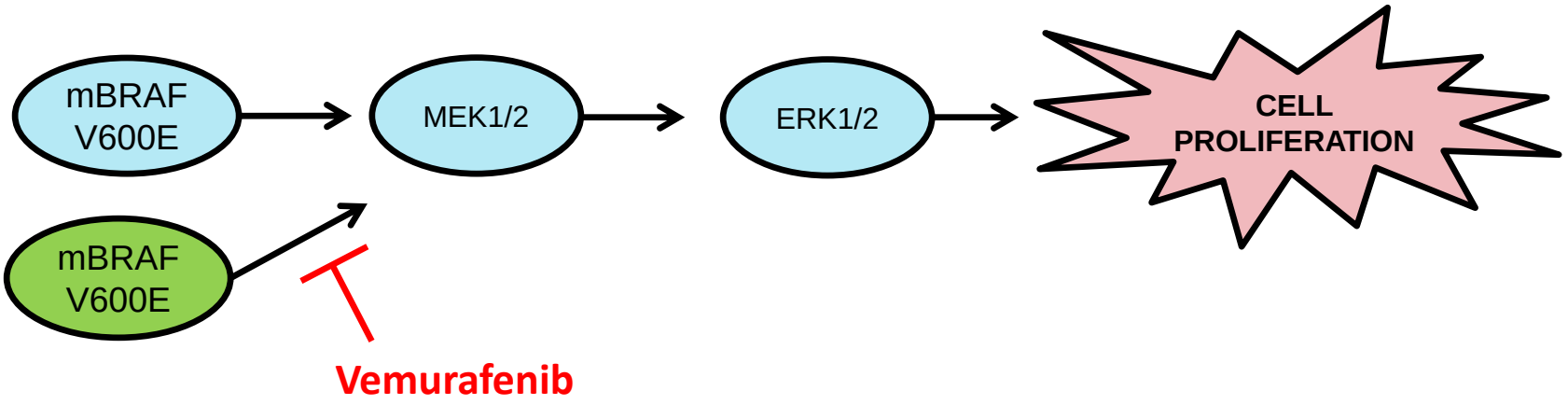


- Phosphorylated retinoblastoma protein (pRb)
  - Direct measure of CDK4/6 inhibition
  - Cell density in late G1 phase
- Topoisomerase II a (TopoIIa)
  - Cell density in S phase
- Phosphohistone H3 (pHH3)
  - Cell density in G2/M phase

Lilly | ONCOLOGY

Vemurafenib Mechanism of Action

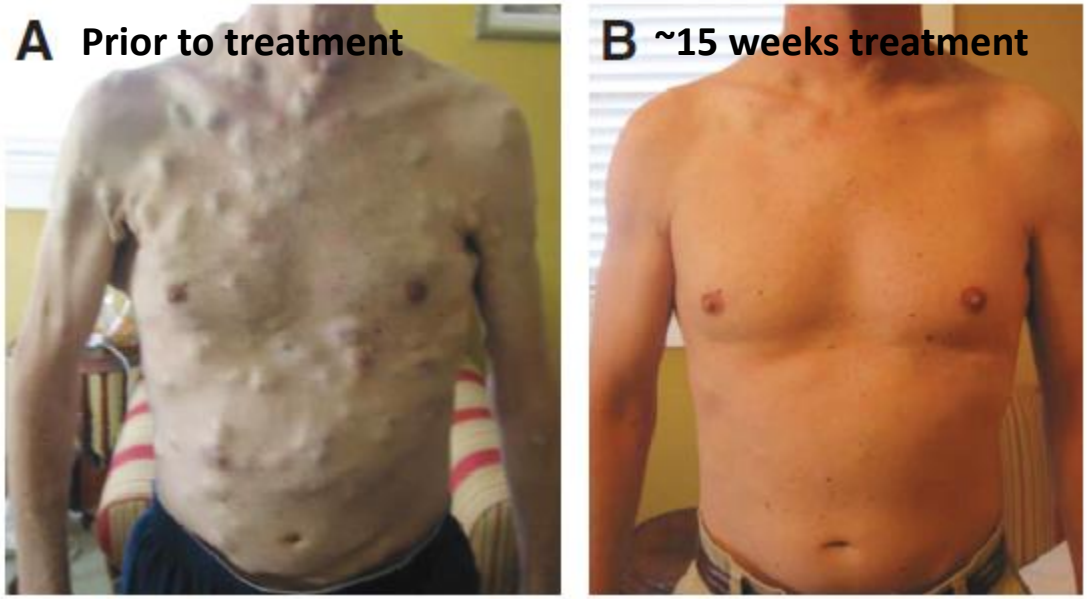
- Vemurafenib is a BRAF inhibitor approved for first-line treatment of BRAF-mutated metastatic (or unresectable) melanoma
  - Vemurafenib interrupts the BRAF/MEK step in the MAPK pathway
  - Vemurafenib is efficacious in patients whose melanoma has become dependent on hyperactive BRAF for survival



- Phosphorylated MEK (pMEK) and ERK (pERK) are direct markers of vemurafenib-mediated inhibition of BRAF

Resistance to Vemurafenib

- While vemurafenib is highly effective in the target population, resistance to treatment occurs readily and rapidly
- Treatment of vemurafenib-resistant melanoma represents an area of unmet medical need

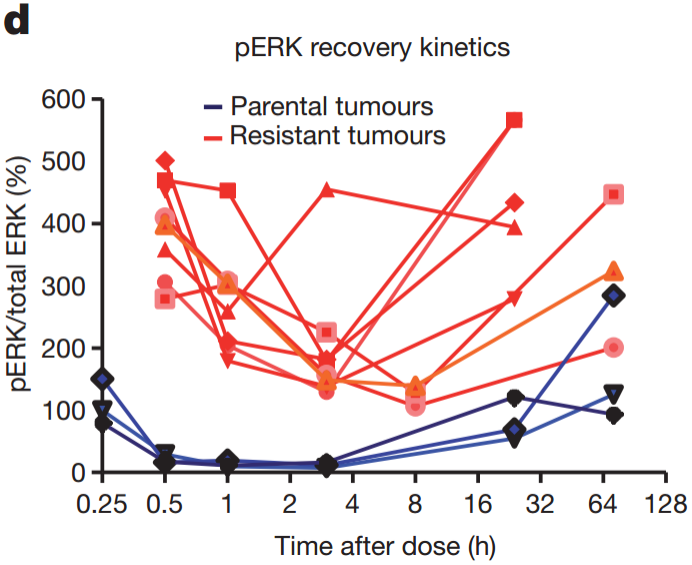


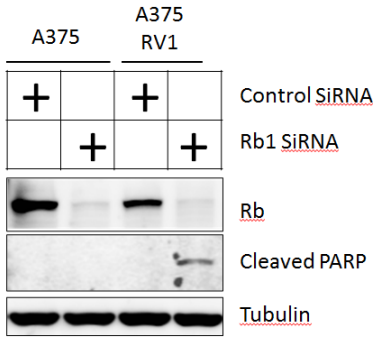
Wagle et al., J Clin Oncol, 2011

Resistance to Vemurafenib: Biological Basis

- Resistant xenograft tumours over-express pERK[1]
  - Resistant baseline levels of pERK are elevated
  - Vemurafenib-mediated inhibition still occurs
  - pERK levels remain above baseline at maximum inhibition

- In house investigations revealed[2]:
  - Resistance is associated with MAPK pathway reactivation and cyclin D1 upregulation
  - Inhibition of CDK4/6 (by abemaciclib) overcomes resistance and induces apoptosis
  - Cells appear to become dependent on Rb for survival; inhibition of Rb by abemaciclib is thought to mediate apoptosis





[1]Thakur et al., Nature, 2014; [2]Vipin et al., Mol Cancer Ther, 2013

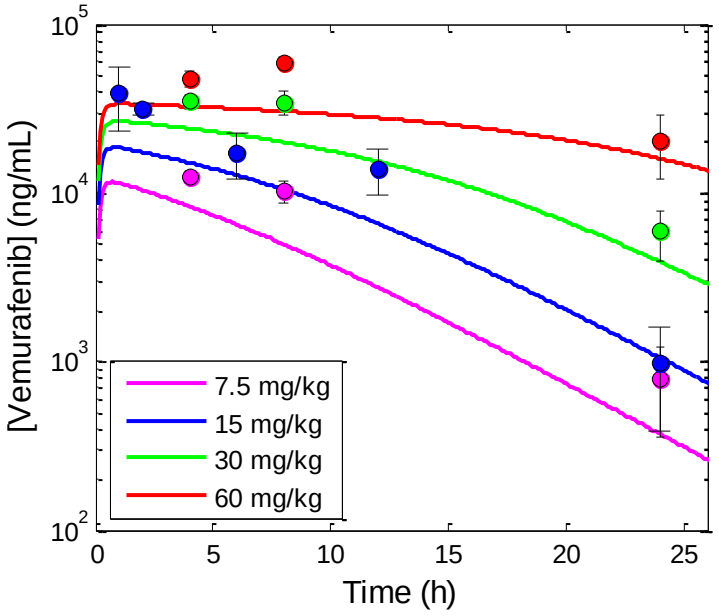
Available Pre-Clinical Data

Drug(s)	Design	Data
Abemaciclib	45 and 90 mg/kg QDx1 1,6,24,36,48 h	PK, biomarkers (pRb, TopoIIα, pHH3, Total Rb)
Vemurafenib	15 mg/kg QDx1 1,2,6,12,24,48 h	PK, (pMEK, pERK, CyclinD1, pRb, TopoIIα, pHH3, Total Rb)
	7.5, 30 and 60 mg/kg QDx1 4,8,24 h	
Vemurafenib, abemaciclib	Control, Vemurafenib 15 mg/kg BIDx76, Vemurafenib 15 mg/kg BIDx48 **then** abemaciclib 90 mg/kg QDx28	Tumour growth

Abemaciclib and Vemurafenib PK Models

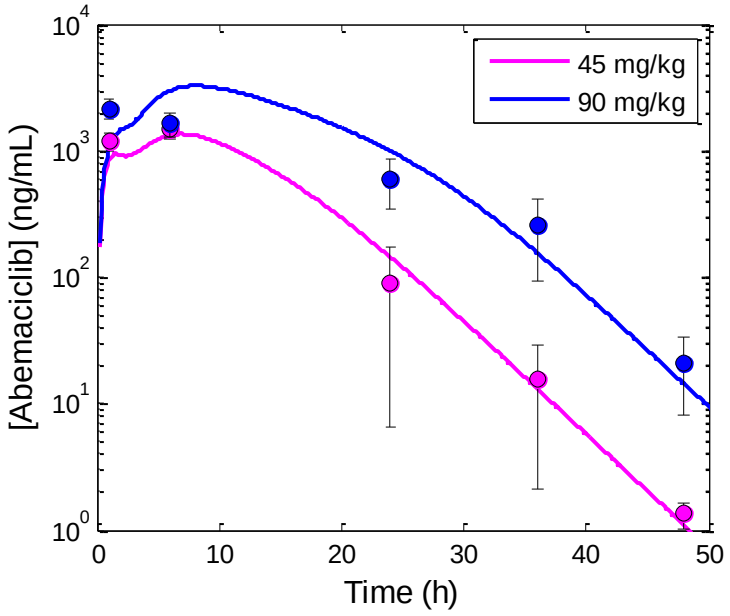
Vemurafenib

- Single dose study (7.5 – 60 mg/kg)
- One compartment model with non-linear absorption and linear clearance



Abemaciclib

- Simulation of previously developed mouse PK model[1]
- Additional PK study confirmed lack of DDI

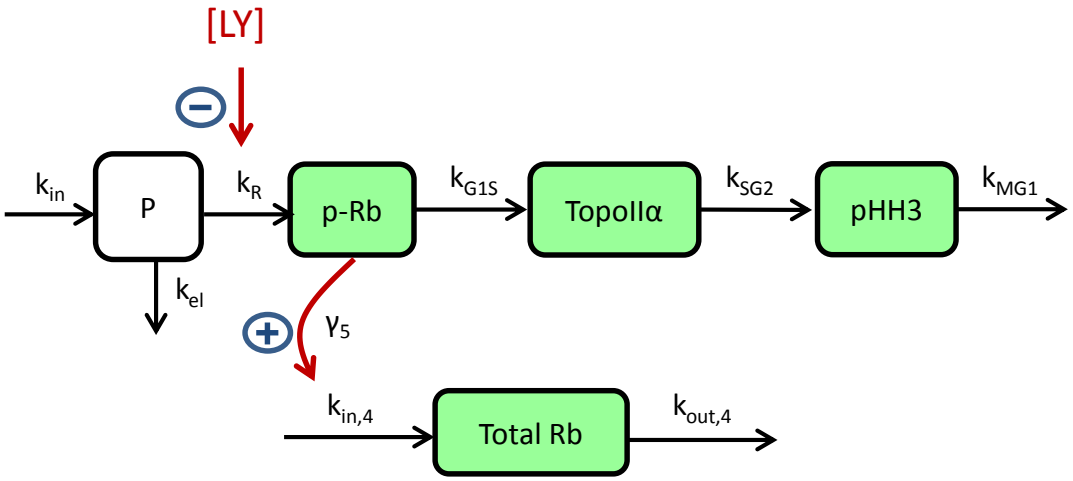


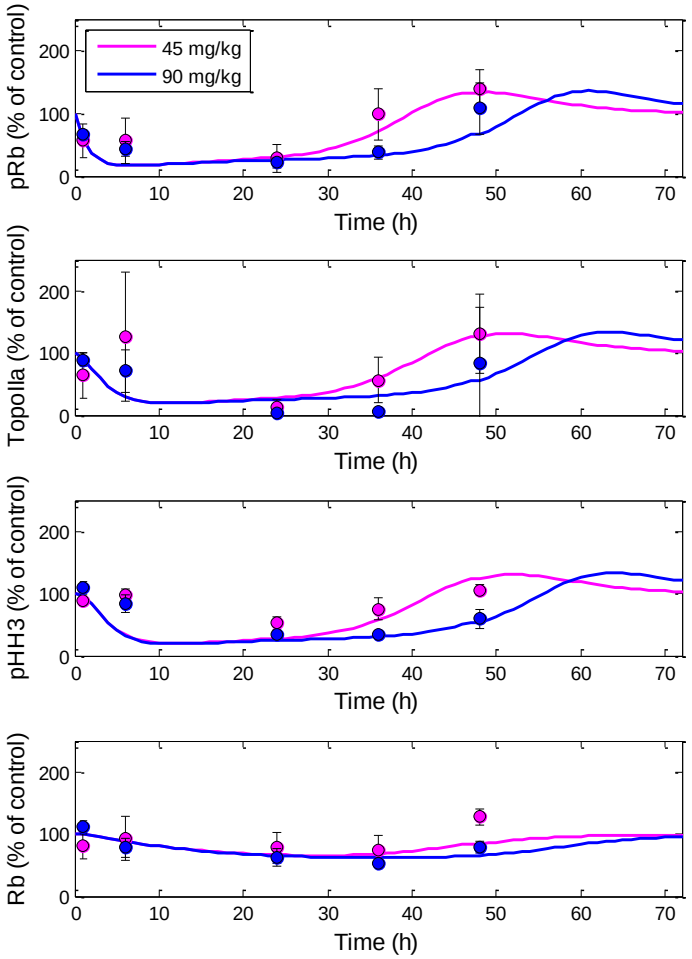
[1]Tate et al., Clin Cancer Res, 2014.

Lilly | ONCOLOGY

Abemaciclib Biomarker Model

- Previously established model[1]; adapted to include autoregulation of total Rb[2]
- Parameterisation based on cell cycle distribution allows recalibration to cell line of interest: A375
- Simulations confirmed accurate model prediction of response to abemaciclib in A375 xenograft tumours

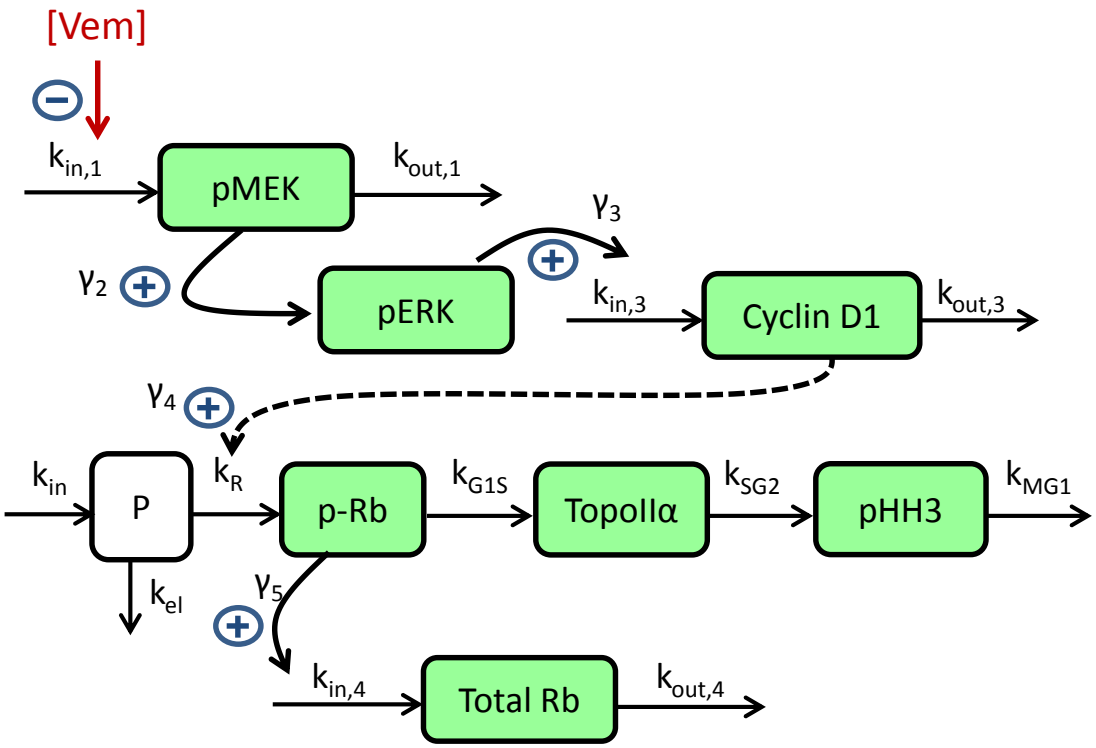


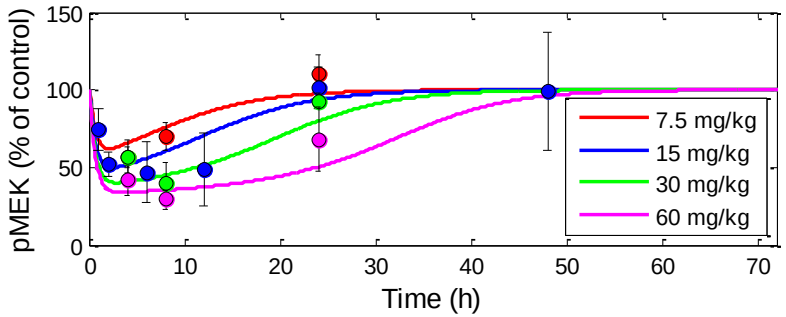


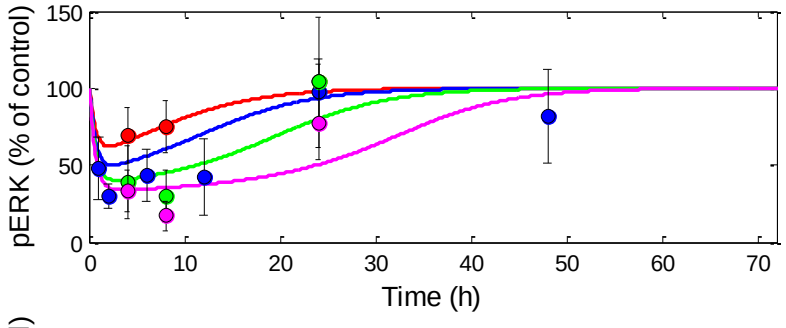
[1]Tate et al., Clin Cancer Res, 2014; [2]Shan et al., Mol Cell Biol, 1994

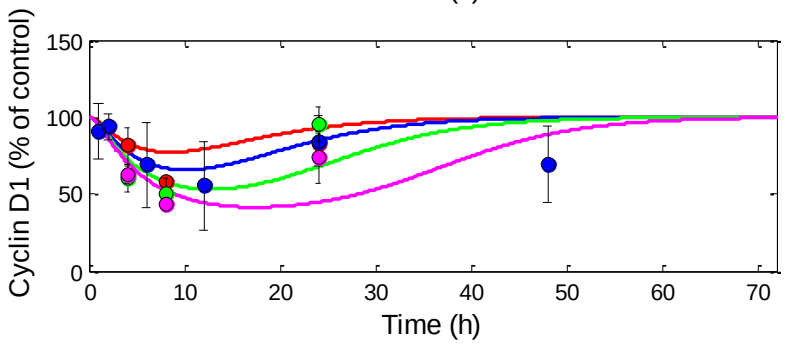
Vemurafenib Biomarker Model

- Model combines elements of MAPK pathway and cell cycle markers
- Cell cycle model structure echoes previously established model for abemaciclib



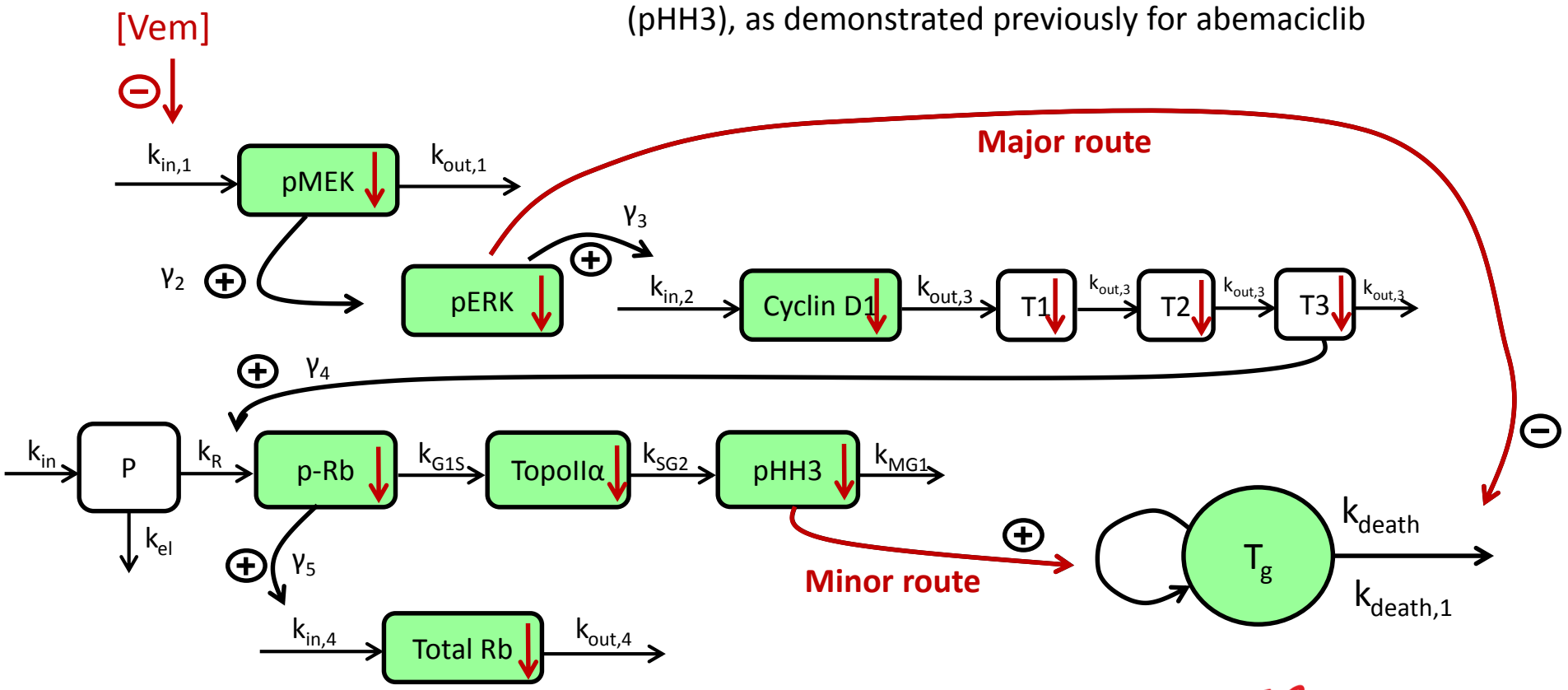






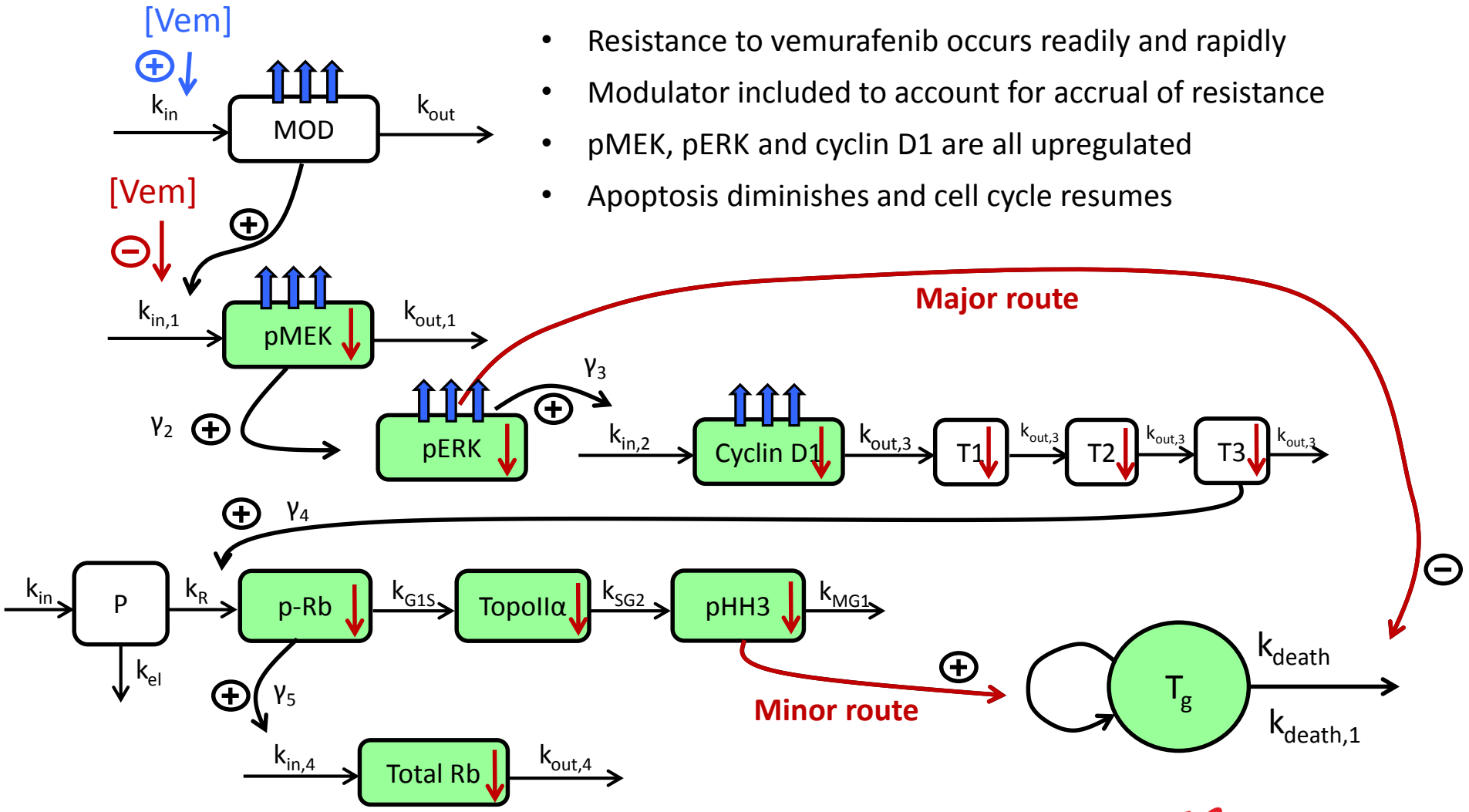
Efficacy Mediated by Vemurafenib

- The anti-tumour effects of vemurafenib are mediated by…
- …Tumour shrinkage caused by inhibition of pERK…
- …And tumour growth inhibition as a result of cell cycle arrest (pHH3), as demonstrated previously for abemaciclib



Accruing Resistance to Vemurafenib

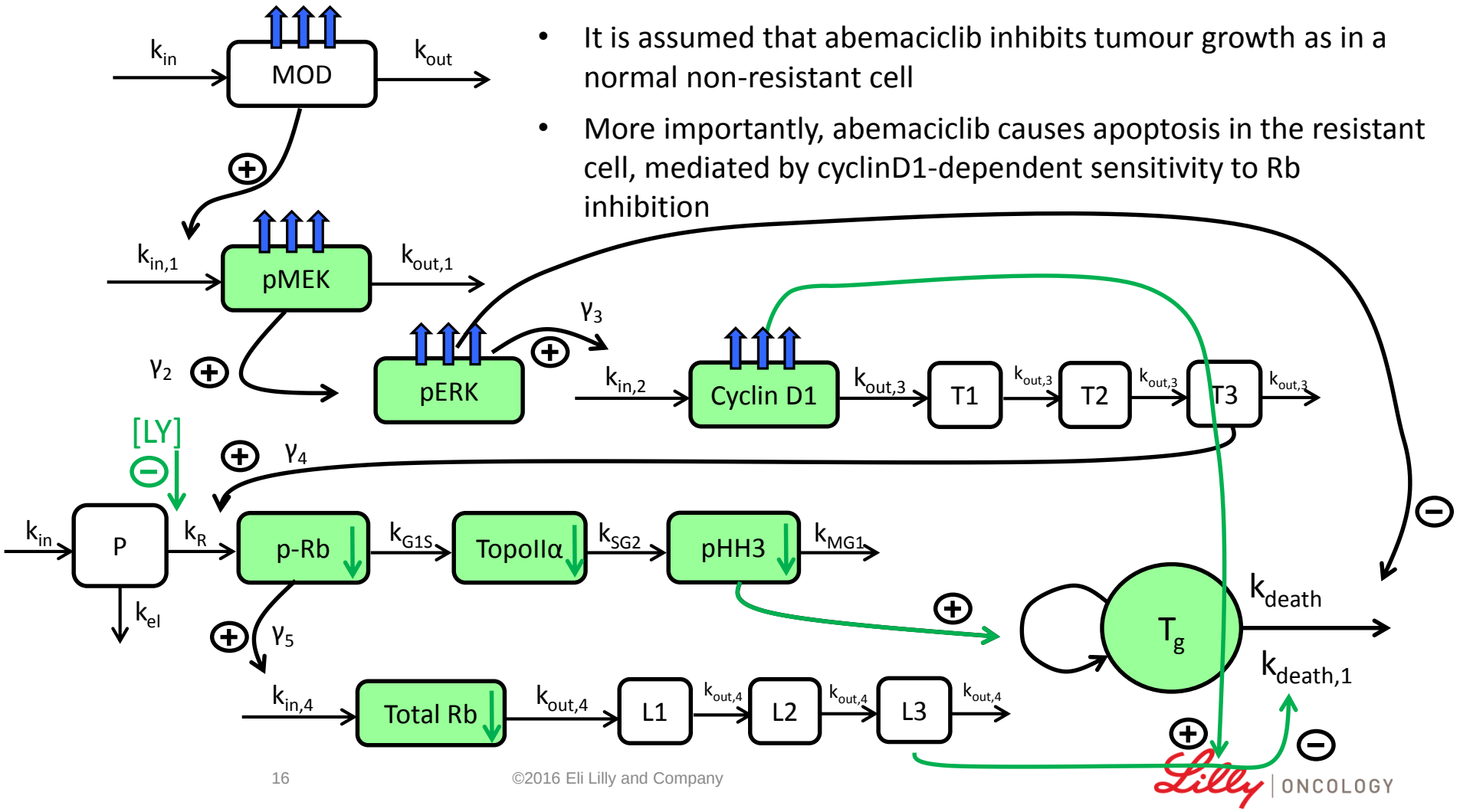
- Resistance to vemurafenib occurs readily and rapidly
- Modulator included to account for accrual of resistance
- pMEK, pERK and cyclin D1 are all upregulated
- Apoptosis diminishes and cell cycle resumes



Lilly | ONCOLOGY

Overcoming Resistance by Abemaciclib

- Abemaciclib overcomes resistance to vemurafenib
- It is assumed that abemaciclib inhibits tumour growth as in a normal non-resistant cell
- More importantly, abemaciclib causes apoptosis in the resistant cell, mediated by cyclinD1-dependent sensitivity to Rb inhibition



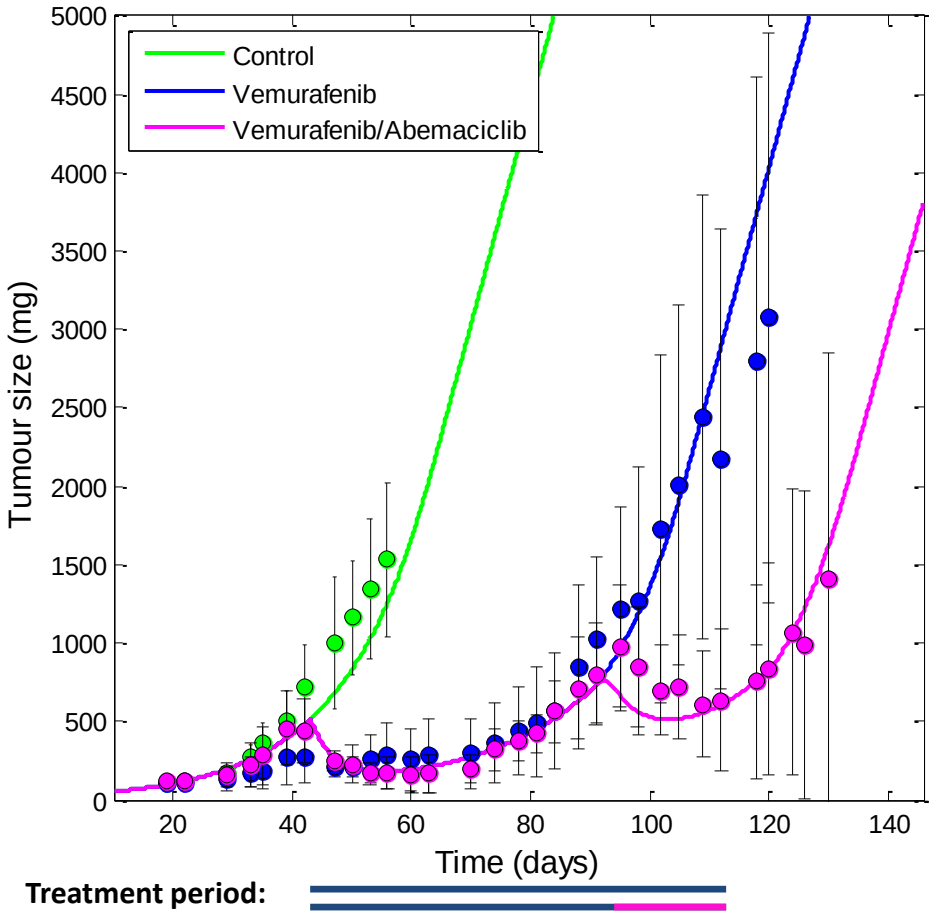
Abemaciclib/Vemurafenib PK/PD Model

Dosing groups:

- Vehicle
- Vemurafenib 15 mg/kg BIDx76
- Sequential vemurafenib 15 mg/kg BIDx48, then abemaciclib 90 mg/kg QDx28

Model accurately describes:

- Uncontrolled tumour **growth**
- Tumour **shrinkage** in the presence of vemurafenib
- Developing **resistance** to vemurafenib
- **Rescue** by abemaciclib



PK/PD Model: Validation

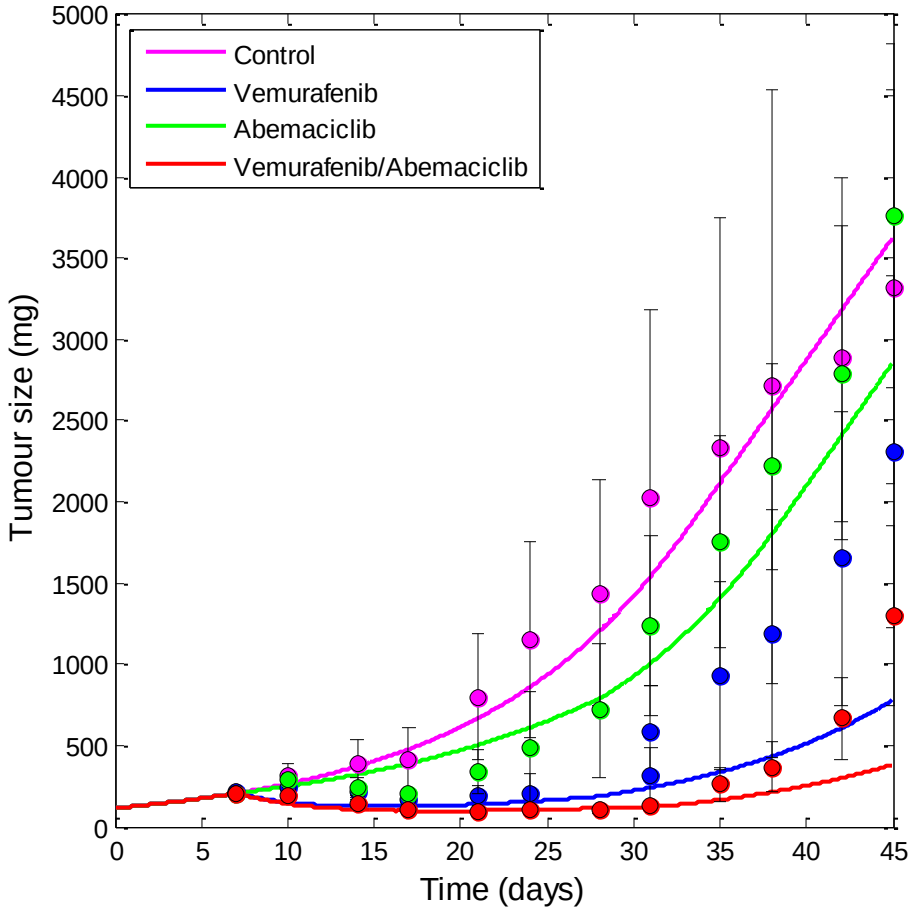
Dosing groups:

- Vehicle
- Vemurafenib 10 mg/kg BIDx21
- Abemaciclib 45 mg/kg QDx21
- Simultaneous vemurafenib 10 mg/kg BIDx21 and abemaciclib 45 mg/kg QDx21

Model accurately describes:

- Uncontrolled tumour growth (fitted)
- Efficacy of abemaciclib and vemurafenib alone and in combination (simulated)
  - Note: short duration of therapy – cells not yet resistant

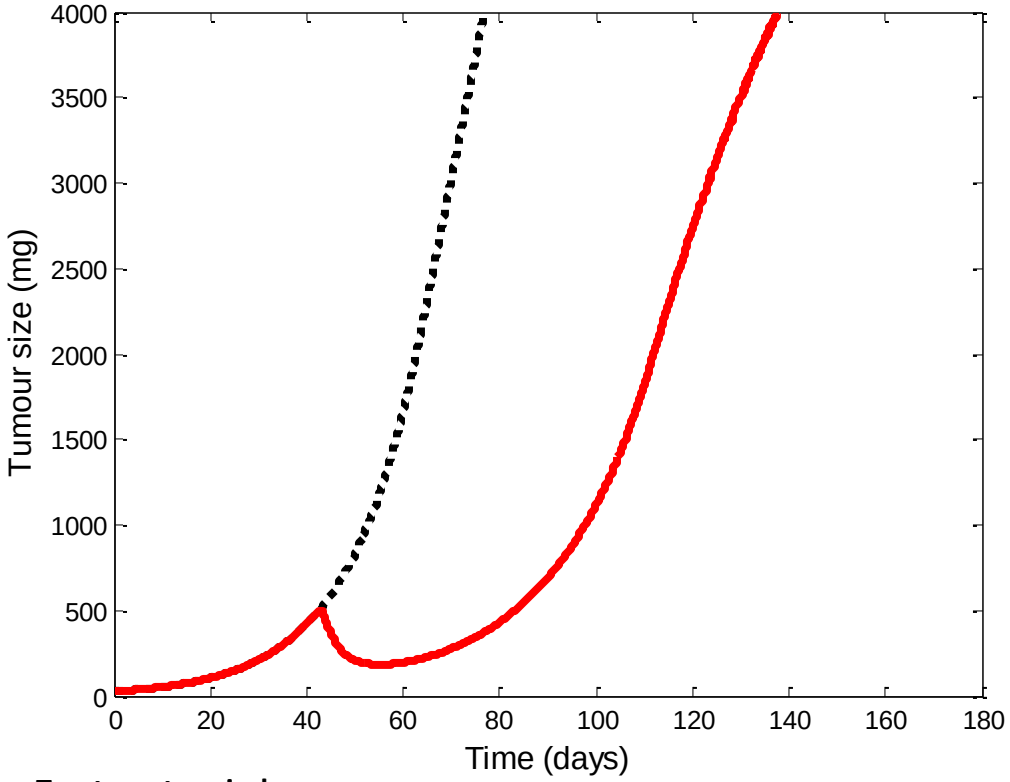
- Provides an external validation of the combination PK/PD model



Lilly | ONCOLOGY

Simulations of Dosing Scenarios

- Vemurafenib treatment is initially efficacious, but resistance soon occurs and tumours regrow

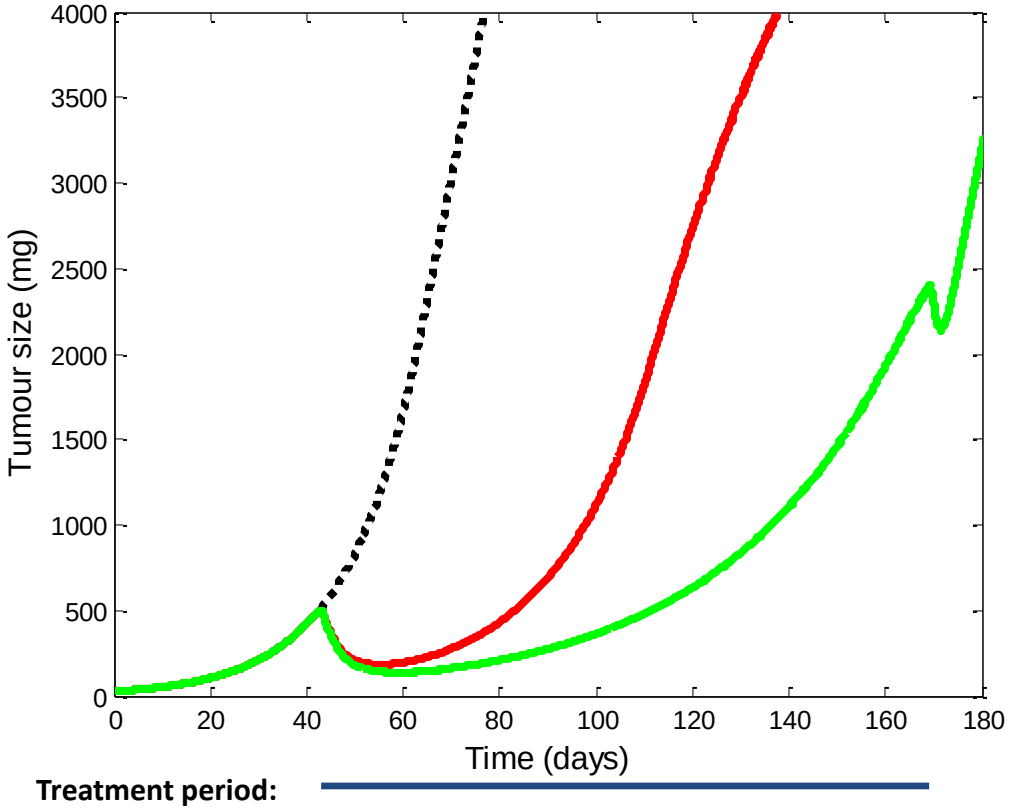


Control growth

Vemurafenib 15 mg/kg BID, **continuous** dosing

Simulations of Dosing Scenarios

- Simultaneous treatment of abemaciclib with vemurafenib (both dosed continuously) offers additional benefit over vemurafenib alone



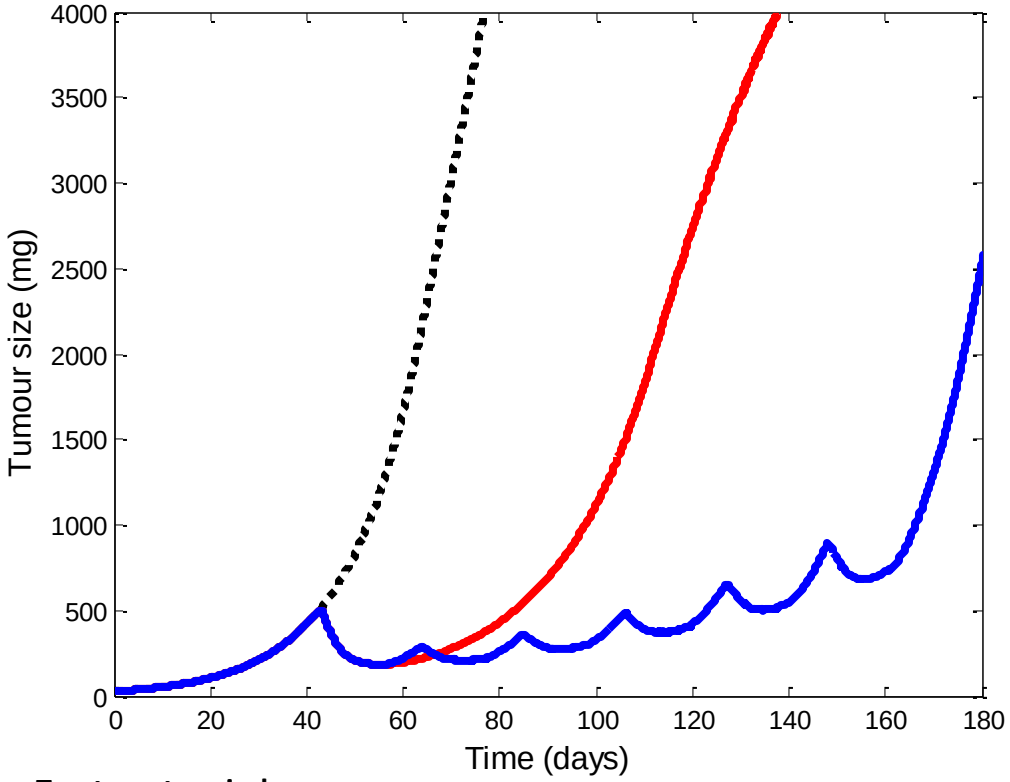
Control growth

Vemurafenib 15 mg/kg BID, **continuous** dosing

Vemurafenib 15 mg/kg BID and abemaciclib 50 mg/kg QD **both continuous** dosing

Simulations of Dosing Scenarios

- Intermittent treatment with vemurafenib delays onset of resistance, thereby extending time to progression[1]



Control growth

Vemurafenib 15 mg/kg BID, **continuous** dosing

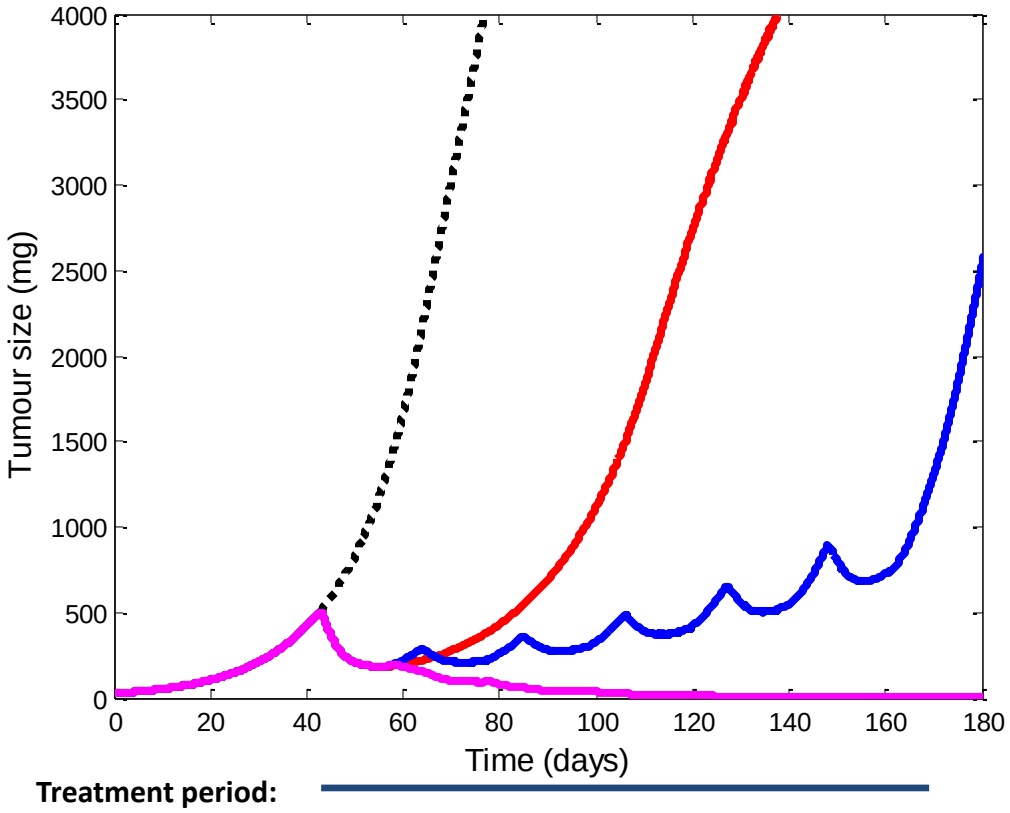
Vemurafenib 15 mg/kg BID, **intermittent** dosing (2 on, 1 off)

[1]Thakur et al., Nature, 2014

Lilly | ONCOLOGY

Simulations of Alternative Dosing Scenarios

- Simultaneous treatment of abemaciclib (continuous) with vemurafenib (intermittent) offers the most efficacious dosing schedule



Control growth

Vemurafenib 15 mg/kg BID, **continuous** dosing

Vemurafenib 15 mg/kg BID, **intermittent** dosing (2 on, 1 off)

Vemurafenib 15 mg/kg BID, **intermittent** dosing (2 on, 1 off), and abemaciclib 50 mg/kg QD continuous

Lilly | ONCOLOGY

Conclusions

- An abemaciclib/vemurafenib pre-clinical PK/PD model was established, describing:
  - Vemurafenib-mediated pERK inhibition, leading to apoptosis
  - Upregulation of the MAPK pathway, resulting in resistance to vemurafenib
  - Increased sensitivity to abemaciclib-mediated inhibition of total Rb when cyclin D1 is upregulated, resulting in apoptosis in the resistant cell

- The model was simulated in various ways to achieve:
  - External validation, by simulating mono- and combo-therapy arms and comparing to observed data
  - Further evidence of the benefit of intermittent vemurafenib dosing to delay onset of resistance
  - Support for combining continuous abemaciclib with intermittent vemurafenib to achieve excellent response in A375 melanoma xenograft tumours

- Future directions
  - The modelling efforts demonstrated the utility of semi-mechanistic PK/PD models in exploring combination therapies
  - Work is ongoing to identify projects which may significantly benefit from such analyses

Final Thoughts

- The benefits of developing semi-mechanistic PK/PD models to evaluate drug combinations are:
  - Simulate hundreds of dosing scenarios, thereby minimising resource requirements and animal usage
  - Formalise quantitative pharmacology for hypothesis testing
- However, time and experienced personnel are required for model development
- Such models are not routinely developed or implemented in drug development
  - Often rely on in vitro / in vivo screens
  - Often constrained by time available on fast-moving clinical development programs
- Using complex systems pharmacology / biology models, it may be possible to test drug combinations in PK/PD models a priori, removing the need for all but confirmatory in vitro / in vivo studies
  - Further investment and development is required to achieve a priori identification of beneficial combination treatments

Lilly | ONCOLOGY

Acknowledgements

Biology

- Teresa Burke
- Shufen Cai
- Vipin Yadav
- Lawrence Gelbert
- Sheng-Bin Peng
- Richard Beckmann

PK/PD

- Damien Cronier
- Erl Wood PK/PD Group

ADME

- Daisy Hartman
- Palaniappan Kulathaivel