Pre-clinical PK/PD modelling of combination therapies in oncology: abemaciclib and vemurafenib

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Combination Therapies in Oncology

- Combination therapies in oncology have been explored and used for many decades
  - e.g. paclitaxel in combination with platinum-based therapy for first-line metastatic ovarian cancer or gemcitabine in combination with paclitaxel for HER2-negative breast cancer
- Combinations are often first explored in clinical practice; only more recently are combinations explored in pre-clinical testing
- The utility of PK/PD modelling in this area is still being explored
  - How can PK/PD help to better understand and optimise combination therapies?
  - Currently limited to empirical relationships to define additivity/synergy
- Lilly proposed a post-doctoral research opportunity to build a PK/PD platform upon which combination therapies could be explored further

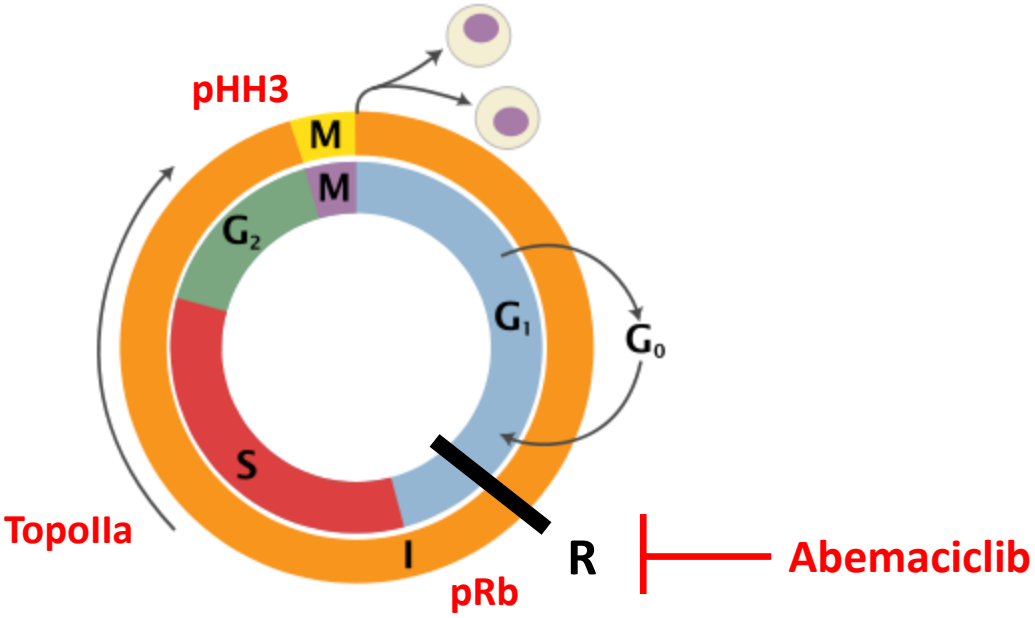
Combination of Abemaciclib and Vemurafenib

- **Abemaciclib** is a CDK4/6 inhibitor currently in clinical development
- The CDK4/6 team were interested in potential combinations which best fit with the current therapeutic strategy
- As melanoma is an indication of interest, the team began looking at the potential benefit of combining abemaciclib with vemurafenib
  - **Vemurafenib** is currently the first-line treatment for patients with BRAF-mutated melanoma
- The semi-mechanistic PK/PD model for abemaciclib[2] presented an opportunity to understand such a combination from a mechanistic, quantitative standpoint

[1]Gelbert et al., Invest New Drugs, 2014; [2]Tate et al., Clin Cancer Res, 2014

Abemaciclib Mechanism of Action

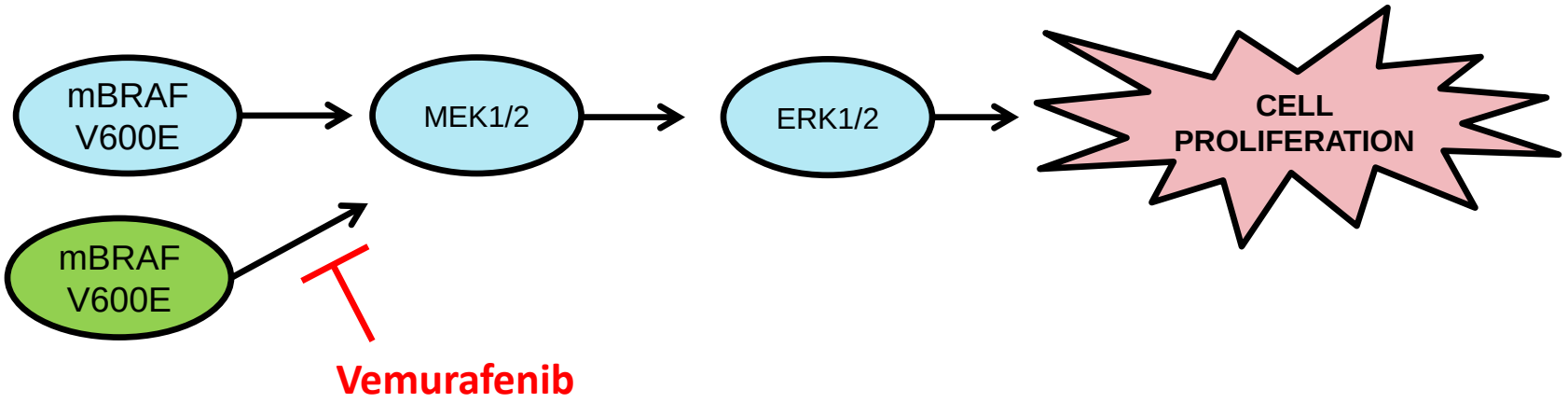
- Abemaciclib is a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) currently in clinical development
  - Abemaciclib-mediated inhibition of CDK4/6 induces cell cycle arrest
  - CDK4/6 inhibition is directly measured by activity of pRb



- 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

Vemurafenib Mechanism of Action

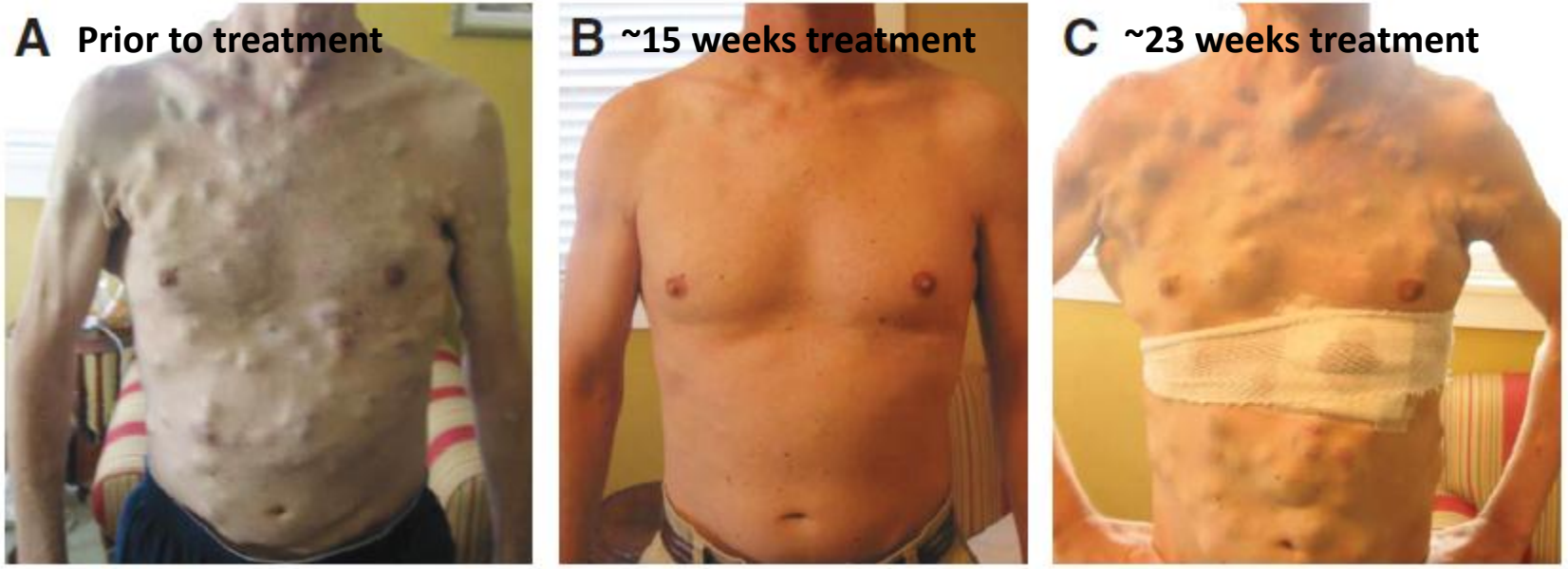
- Vemurafenib is a BRAF inhibitor approved for first-line treatment of BRAF-mutated metastatic (or unresectable) melanoma
  - Vemurafenib interrupts the BRAF/MEK step in the MAPK pathway
  - Vemurafenib is efficacious in patients whose melanoma has become dependent on hyperactive BRAF for survival



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

Resistance to Vemurafenib

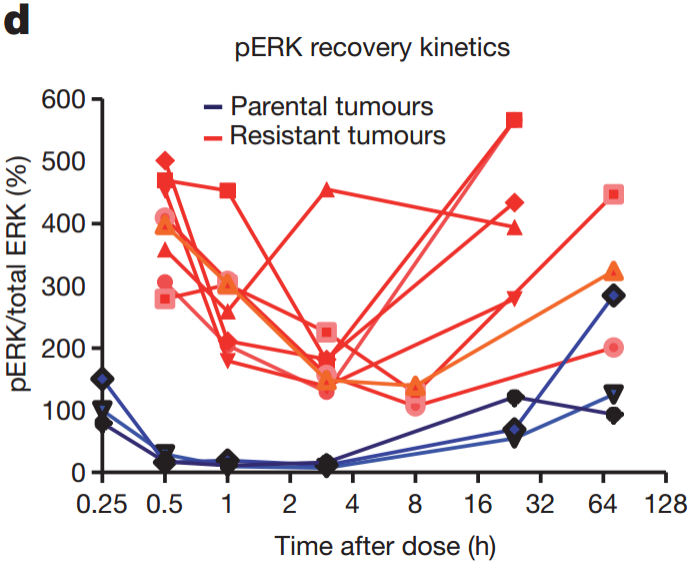
- While vemurafenib is highly effective in the target population, resistance to treatment occurs readily and rapidly
- Treatment of vemurafenib-resistant melanoma represents an area of unmet medical need



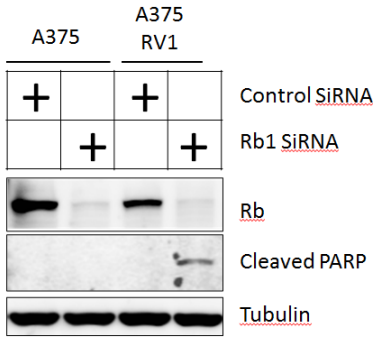
Wagle et al., J Clin Oncol, 2011

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

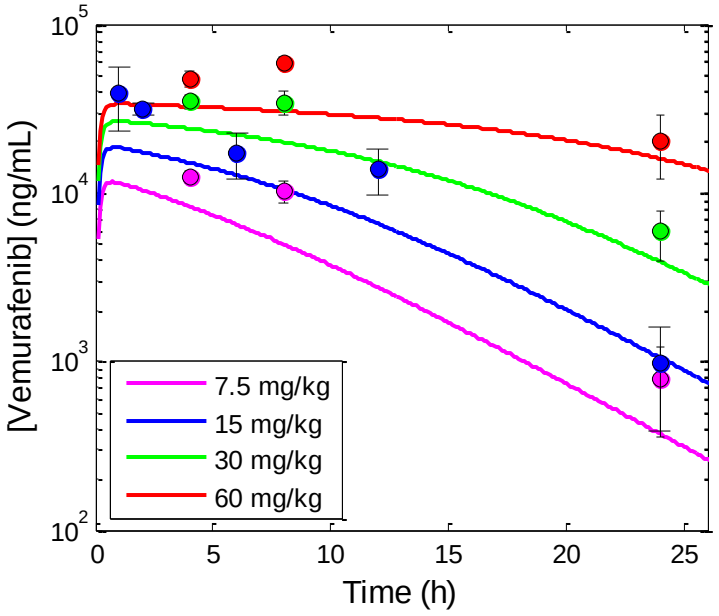
Available Pre-Clinical Data

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

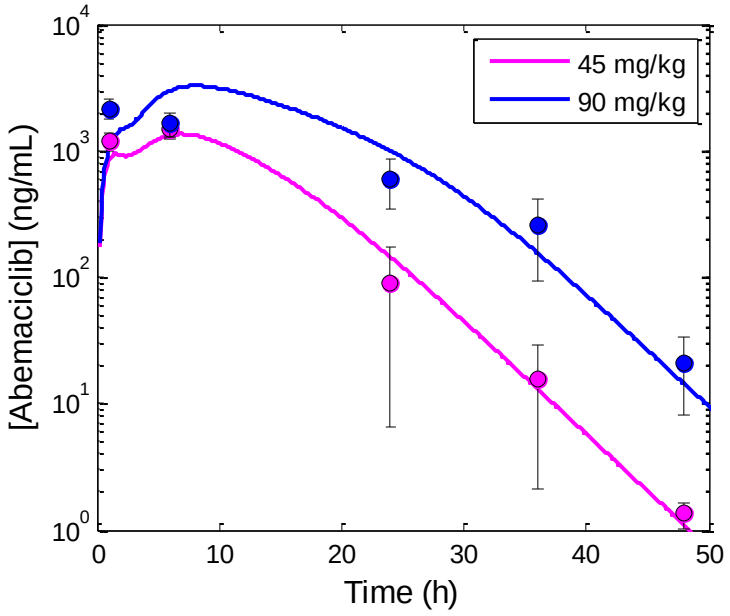
Vemurafenib

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



Abemaciclib

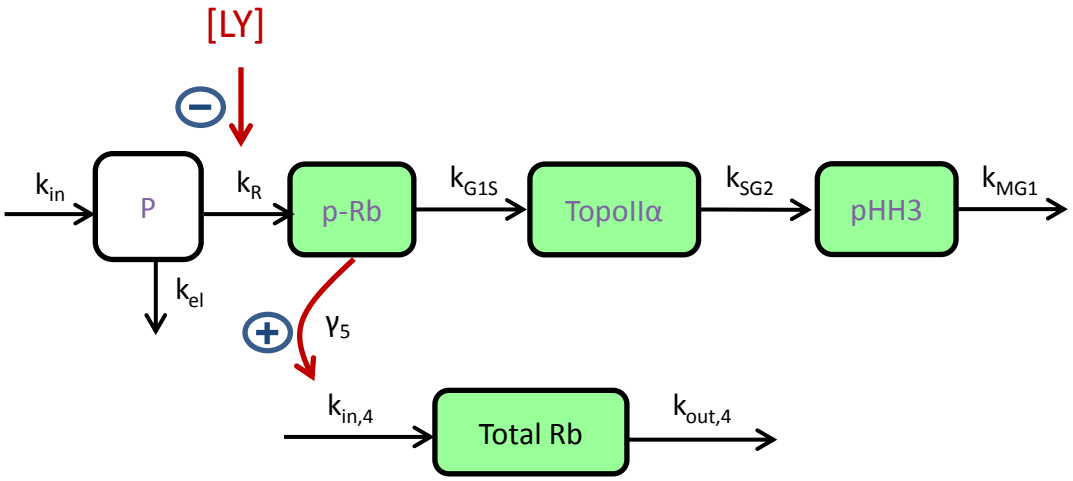
- Simulation of previously developed mouse PK model[1]
- Additional PK study confirmed lack of DDI

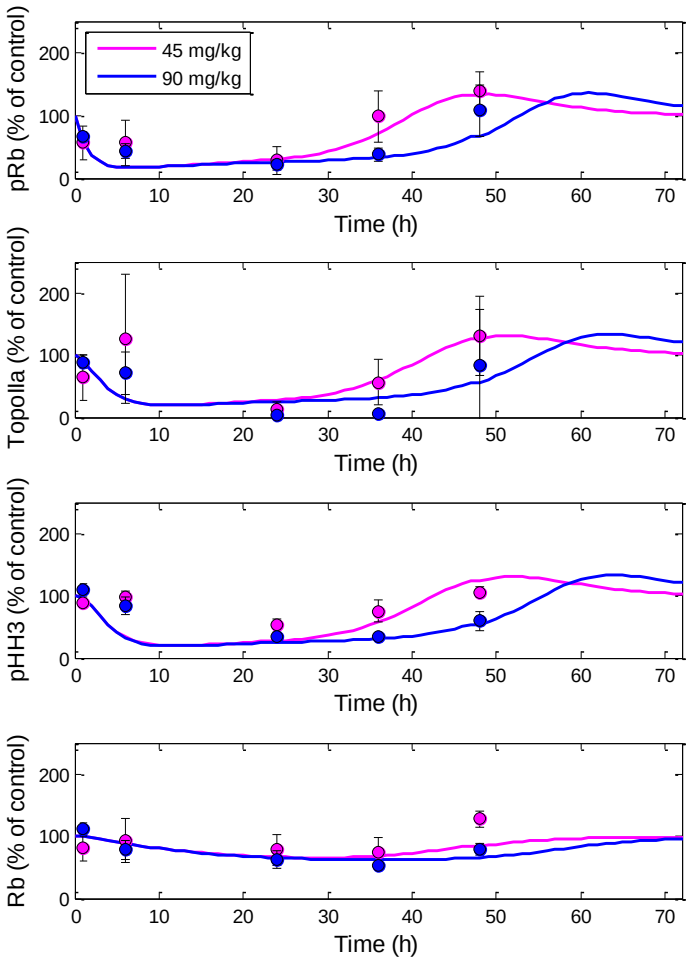


[1]Tate et al., Clin Cancer Res, 2014.

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

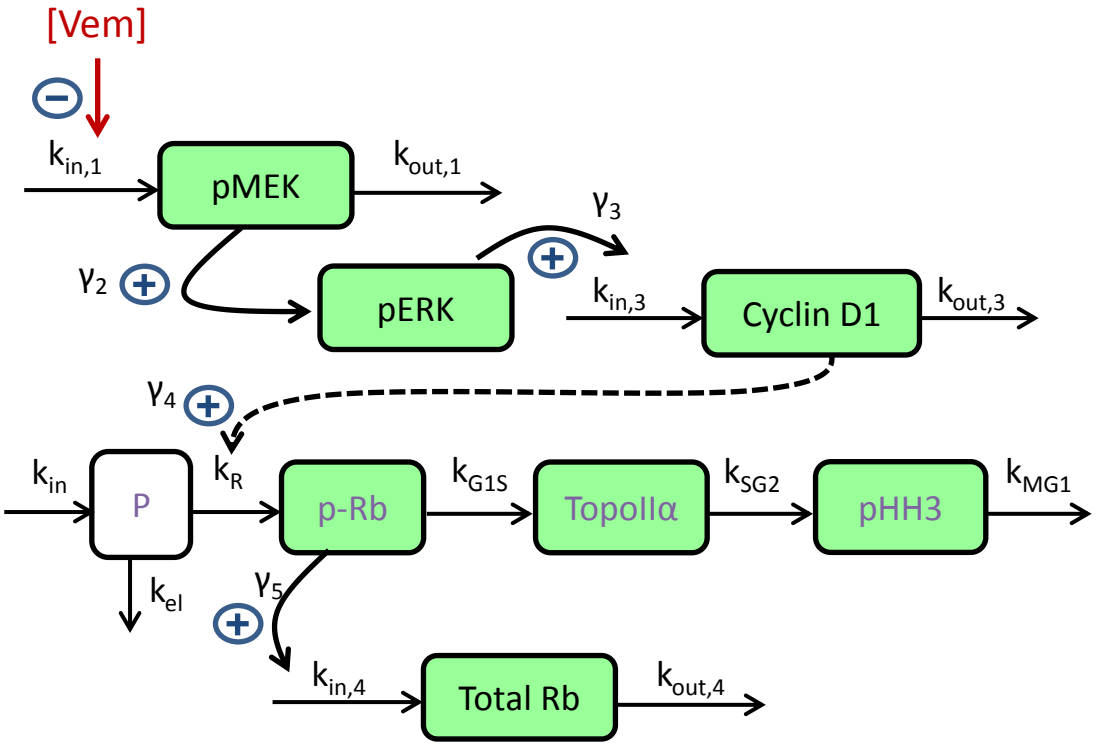


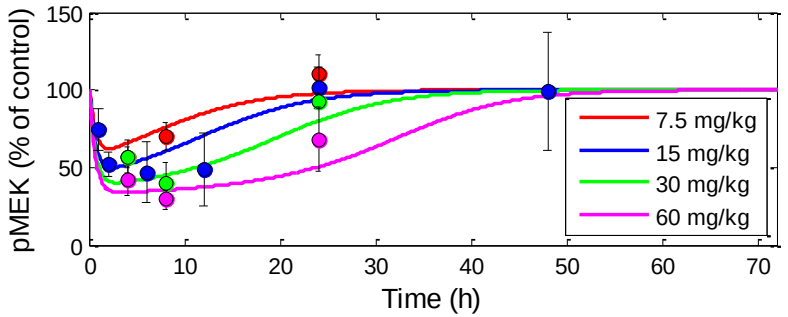


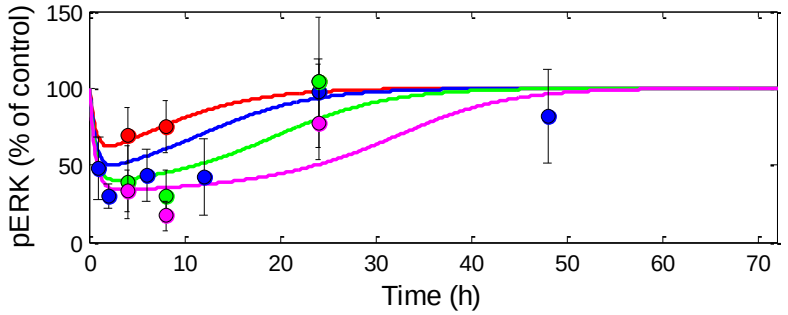
[1]Tate et al., Clin Cancer Res, 2014; [2]Shan et al., Mol Cell Biol, 1994

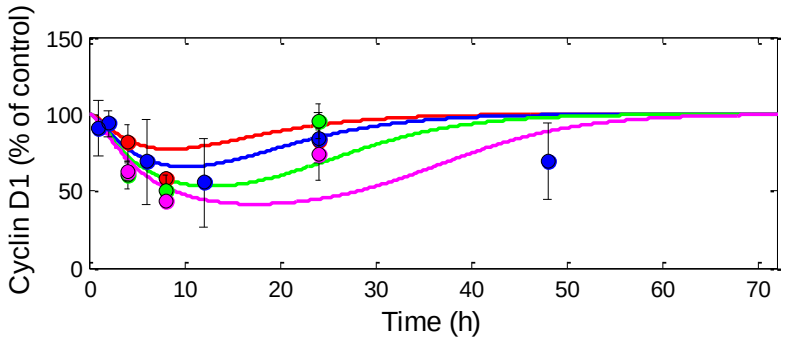
Vemurafenib Biomarker Model

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



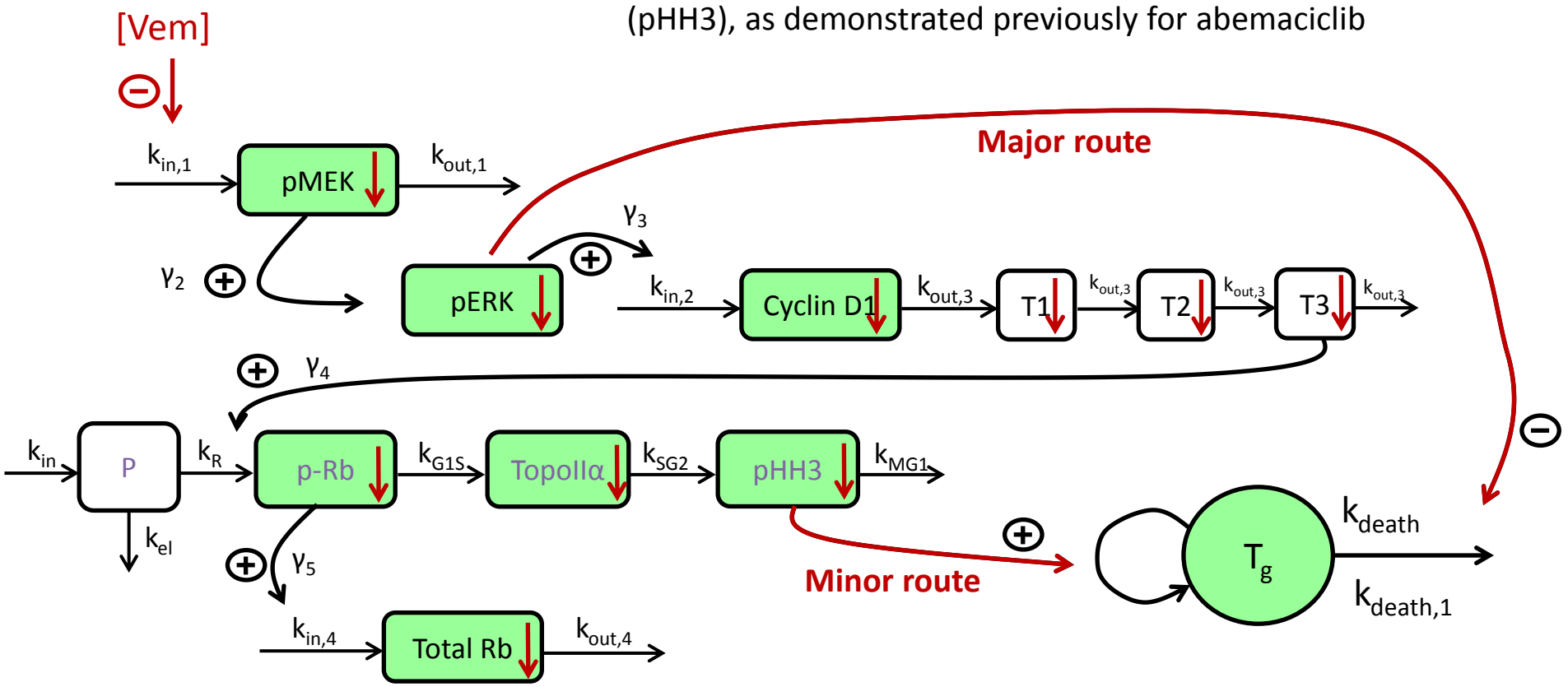






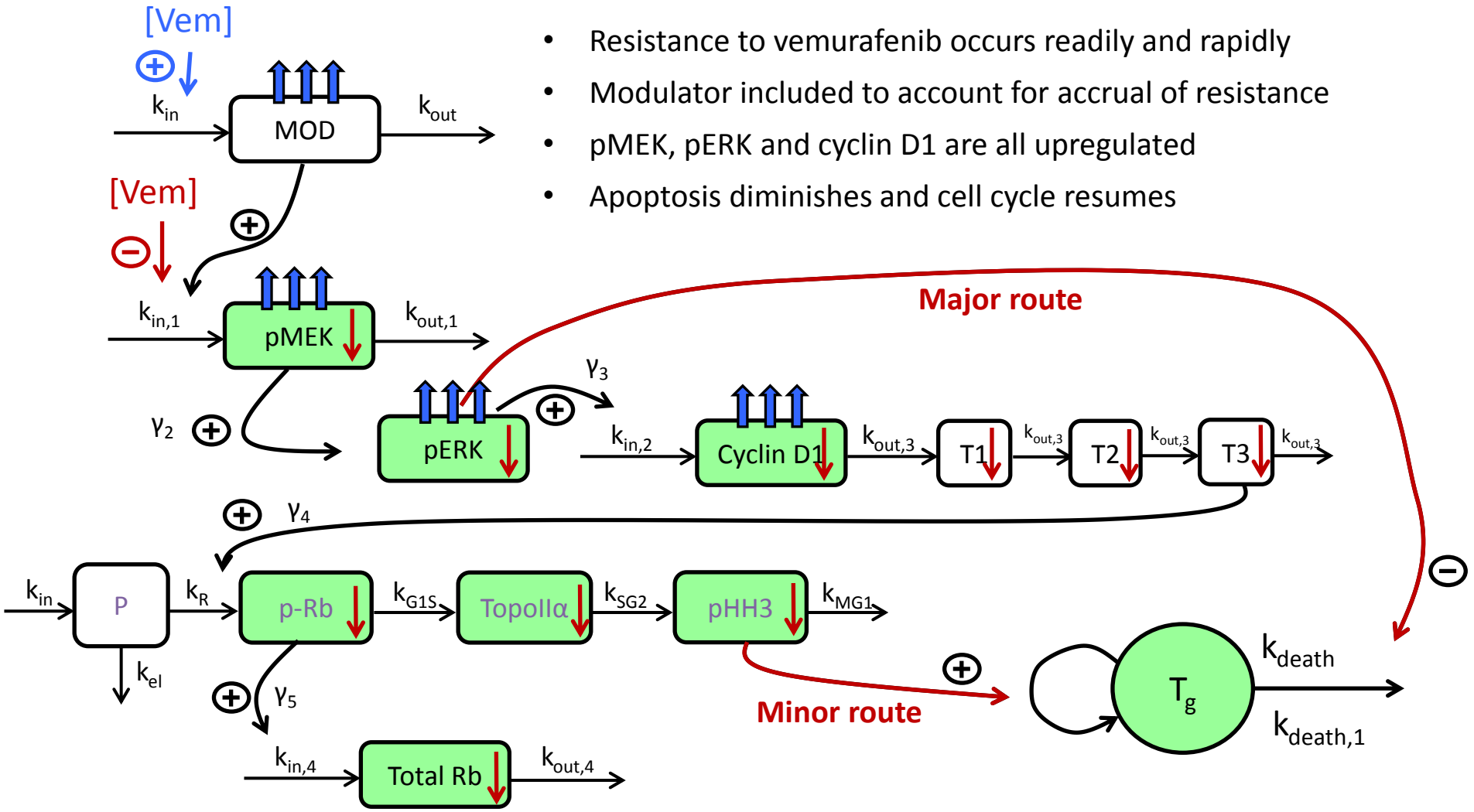
Efficacy Mediated by Vemurafenib

- 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



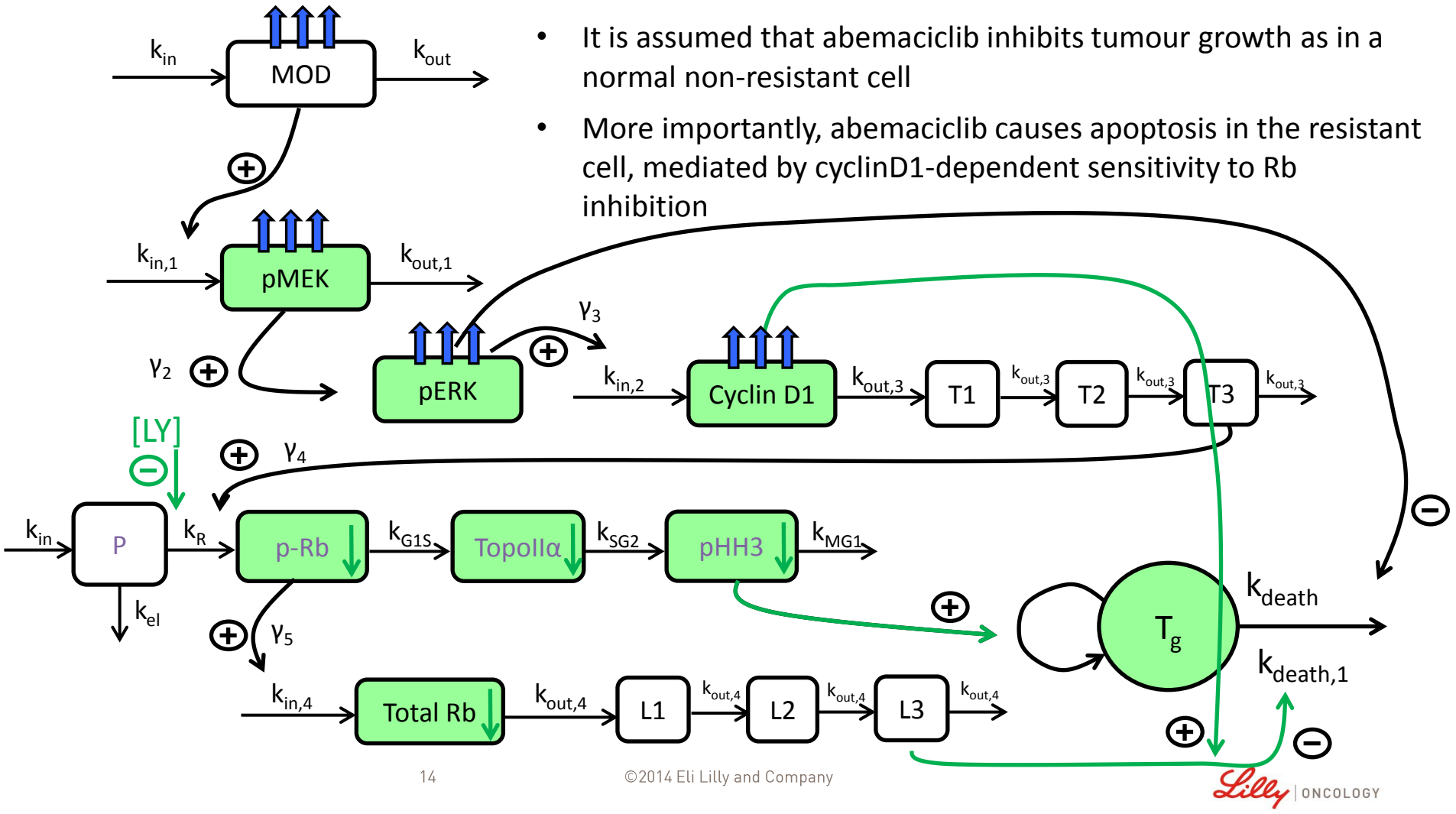
Accruing Resistance to Vemurafenib

- 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



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



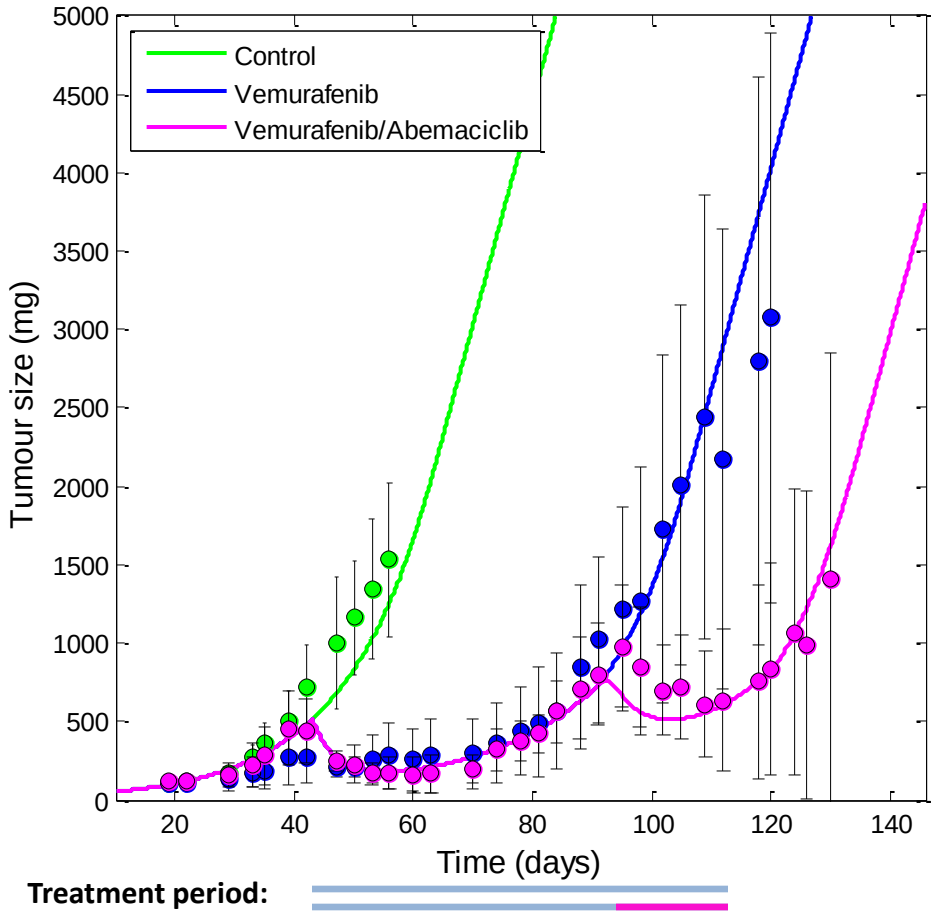
Abemaciclib/Vemurafenib PK/PD Model

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

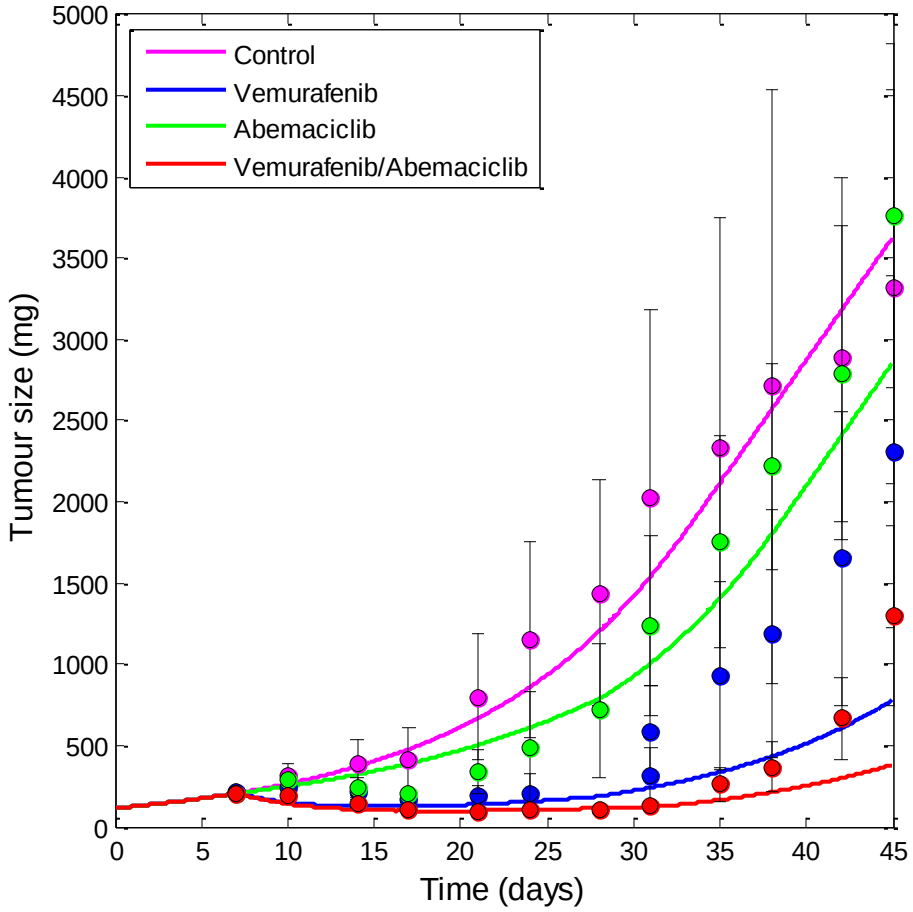
Dosing groups:

- 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:

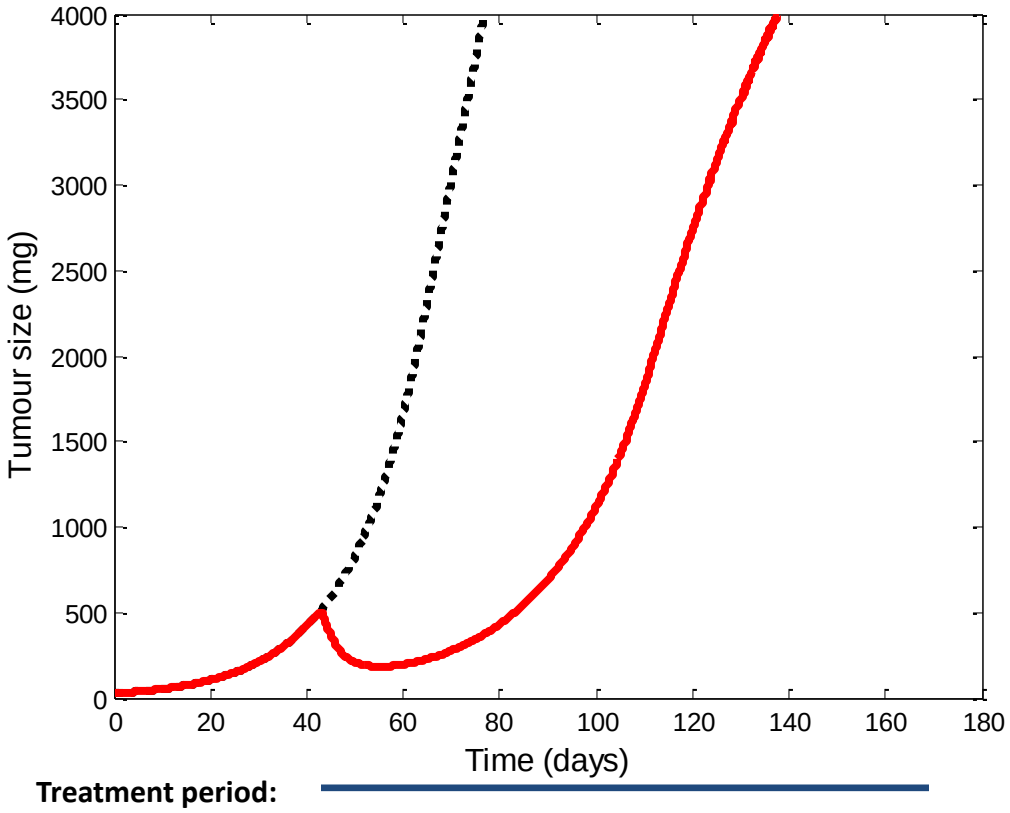
- Uncontrolled tumour growth (fitted)
- Efficacy of abemaciclib and vemurafenib alone and in combination (simulated)
  - Note: short duration of therapy – cells not yet resistant

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



Simulations of Alternative Dosing Scenarios

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

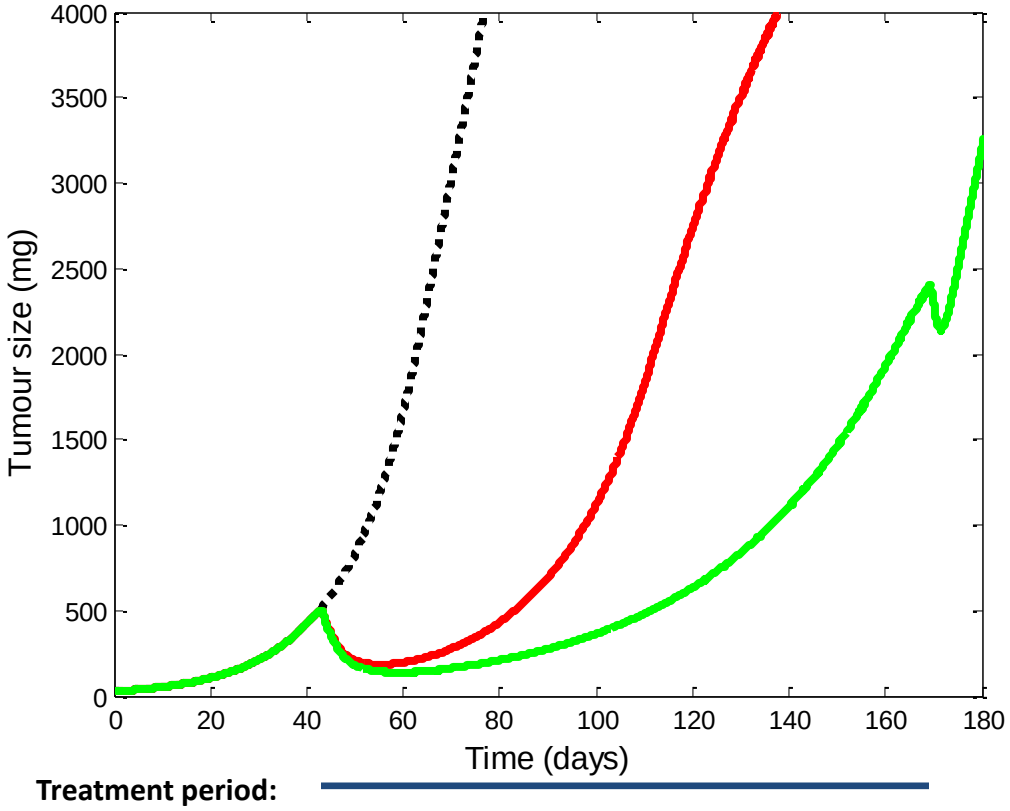


Control growth

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

Simulations of Alternative Dosing Scenarios

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



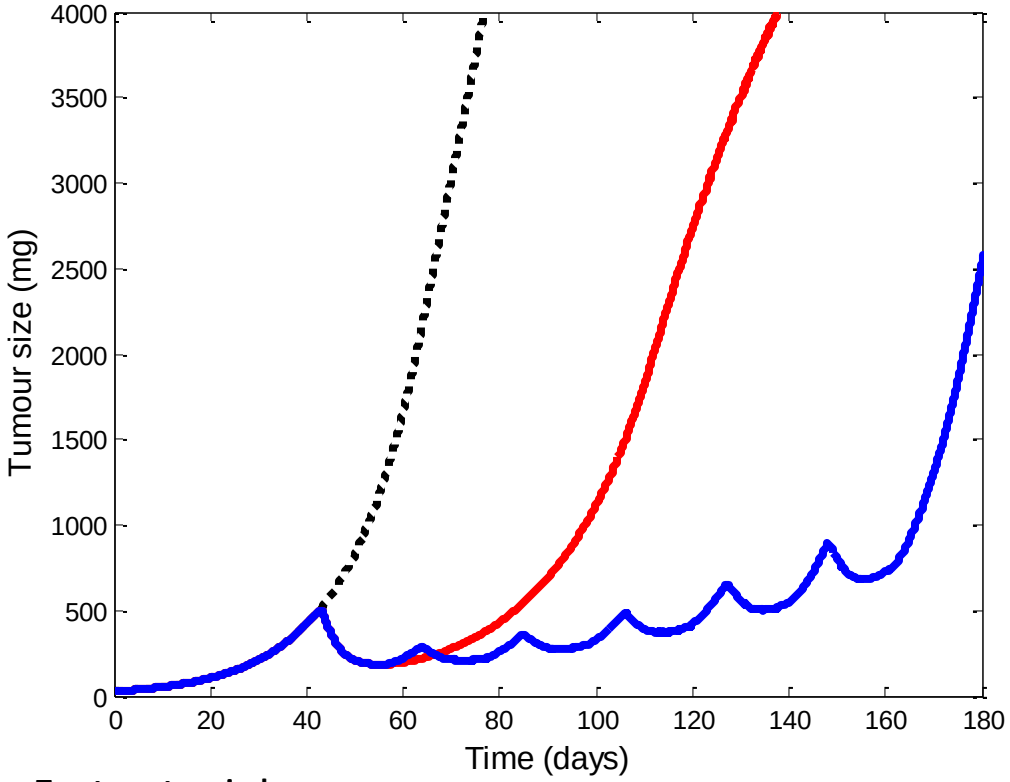
Control growth

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

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

Simulations of Alternative Dosing Scenarios

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



Control growth

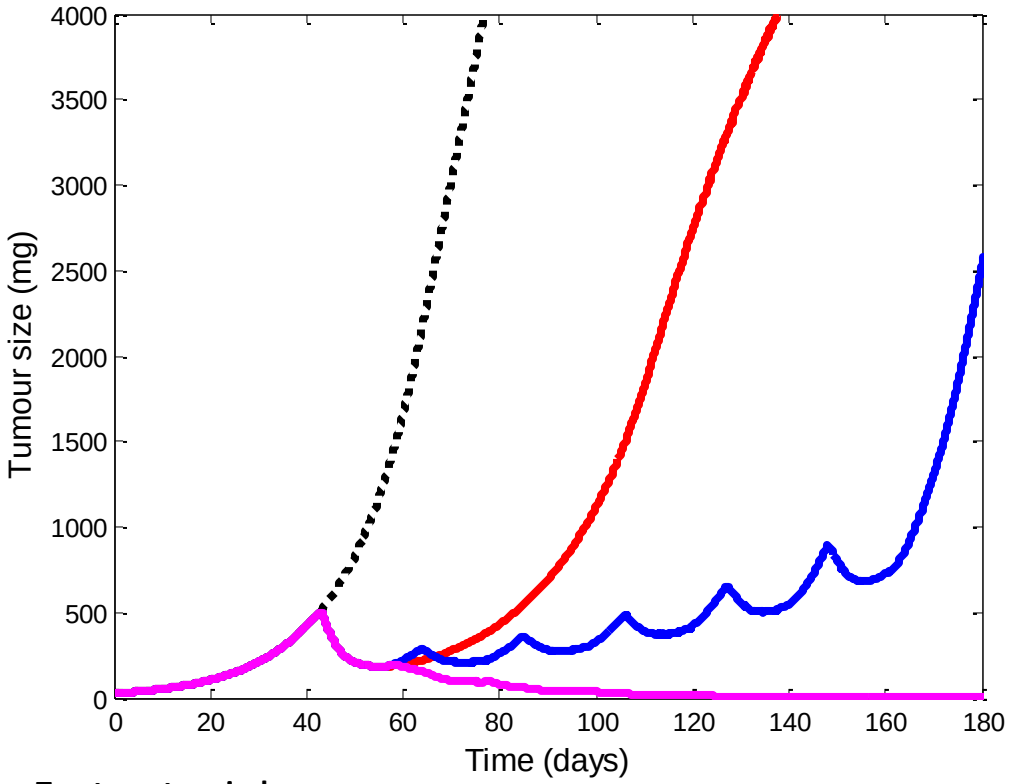
Vemurafenib 15 mg/kg BID, **continuous** dosing

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

[1]Thakur et al., Nature, 2014

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

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

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