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

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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
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]
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 (Topolla)
  - Cell density in S phase

- Phosphohistone H3 (pHH3)
  - Cell density in G2/M phase
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.

Prior to treatment

~15 weeks treatment

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

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

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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

\[\begin{align*}
[LY] & \xrightarrow{k_{in}} P \\
& \xrightarrow{k_R} \xrightarrow{k_{G1S}} p-Rb \xrightarrow{k_{SG2}} \xrightarrow{k_{MG1}} \text{TopoIIa} \xrightarrow{k_{MG1}} \text{pHH3} \\
& \xrightarrow{k_{el}} \xrightarrow{v_S} \xrightarrow{k_{in,4}} \text{Total Rb} \xrightarrow{k_{out,4}} \end{align*}\]

\(^1\)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

\[ \text{Vemurafenib} \]

\[
\begin{align*}
&\text{pMEK} \\
&\text{pERK} \\
&\text{Cyclin D1} \\
&\text{P} \\
&\text{p-Rb} \\
&\text{Topoll}\alpha \\
&\text{pHH3} \\
&\text{Total Rb}
\end{align*}
\]
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

**Diagram Explanation**

- **Major route**:
  - [Vem] modulator included
  - pMEK, pERK, and cyclin D1 are upregulated
  - Apoptosis diminishes, cell cycle resumes

- **Minor route**:
  - pRb, Topollα, pH3, Total Rb, and Tg pathways involved

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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
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 Dosing Scenarios

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

![Graph showing tumor growth and treatment effectiveness](image-url)
Simulations of Dosing Scenarios

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

![Graph showing tumor growth comparison](image)

- Control growth
- Vemurafenib 15 mg/kg BID, continuous dosing
- Vemurafenib 15 mg/kg BID and abemaciclib 50 mg/kg QD both continuous dosing

Treatment period:
Simulations of Dosing Scenarios

- Intermittent treatment with vemurafenib delays onset of resistance, thereby extending time to progression\(^1\)

![Graph showing tumor size over time with different dosing scenarios](image_url)

- 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

![Graph showing tumor growth with different dosing scenarios]

- 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** dosing

Treatment period: [Graph highlight]
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
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