Model Informed Development of Abemaciclib: Collaboration, Computation, and Communication

FDA-ISoP Public Workshop: Model Informed Drug Development (MIDD) for Oncology Products

1 February 2018

Kellie Turner, Pharm.D., Ph.D.
♦ Team
♦ Abemaciclib background
♦ Models informing development and filing
Collaborators

♦ PK/PD/Pharmacometrics
  • Emmanuel Chigutsa
  • Jan-Stefan van der Walt
  • Siva Rama Prasad Kambhampati
  • Damien Cronier
  • Sonya Tate
  • Amanda Sykes
  • Lisa Ferguson-Sells

♦ ADME
  • Maria Posada
  • Gemma Dickinson
  • Steve Hall
  • Palaniappan Kulanthaivel

♦ Clinical Pharmacology
  • Jill Chappell

♦ Dataset creation
  • Gordon Morrow
  • Jin Su

♦ CMC
  • Stephen Stamatis
  • John Rose

♦ Statistics
  • Martin Frenzel
  • Yong Lin
  • Tammy Forrester

♦ Medical
  • Ian Smith

♦ Special Thanks to Study Participants!
Abemaciclib

- CDK 4 & 6 inhibitor approved in HR+ HER2-advanced/metastatic breast cancer based on MONARCH 1 and MONARCH 2
- CYP3A4 substrate
- Active metabolites equipotent to parent and represent ~45% of plasma exposure
- 200 mg orally twice daily (single agent)
- 150 mg orally twice daily (with fulvestrant)
- Dose reductions for individual tolerability in 50 mg units to 50 mg twice daily
Models with a purpose

Dose Justification

Identify a “target” exposure

Pre-clinical PK/PD model

Predict drug interactions not studied

PBPK model

PK Input for Clinical E-R (PK/PD)

Understand therapeutic window

Starting dose and dose reductions

Characterize PK in Patients

PopPK model

Identify patient subgroups who may need dose adjustment (e.g., sex, weight, renal function)

PopPK/PD model
Pre-Clinical PK/PD Model to Identify Potentially Effective Clinical Dose Range

Title:
Semi-Mechanistic Pharmacokinetic/Pharmacodynamic Modeling of the Antitumor Activity of LY2835219, a New Cyclin-Dependent Kinase 4/6 Inhibitor, in Mice Bearing Human Tumor Xenografts

Authors:
Sonya C. Tate, Shufen Cai, Rose T. Ajami, Teresa Burke, Richard P. Beckmann, Edward M. Chen, Alfonso De Dios, Graham N. Wishart, Lawrence M. Gelbert, and Damien M. Cronier

Diagram:
- Gut dose
- Peripheral $V_{Per}$
- Absorption $V_{max}$, $K_m$
- Elimination $V_{max}$, $K_m$
- Central $V_{Can}$
- $t_{max}$, $IC_{50}$
- $k_{in}$
- $p-Rb$
- Topollα
- pH3
- $C_{50}$, $\gamma_2$
- $k_{death}$
- Tumor $w_0$
- Non-growing Tumor
- $\lambda_0$, $\lambda_1$
- $k_{stasis}$

Published Online First May 21, 2014; DOI: 10.1158/1078-0432.CCR-13-2846

Cancer Therapy: Preclinical
Preclinical PK/PD Model Impact

♦ Sustained inhibition of CDK4/6 required for durable cell cycle arrest
♦ Supports a chronic dosing strategy
♦ Selection of a PD biomarker
♦ Identified a target $C_{\text{min,ss}}$ needed to maintain durable cell cycle arrest
Target Exposure and Maximal Target inhibition Achieved at 150 and 200 mg Q12H

A Population Pharmacokinetic and Pharmacodynamic Analysis of Abemaciclib in a Phase I Clinical Trial in Cancer Patients

Sonya C. Tate, Amanda K. Sykes, Palaniappan Kulanthaivel, Edward M. Chan, P. Kellie Turner, Damien M. Cronier

Dose Justification
Identify a "target" exposure
How can we model PK data from multiple studies and manage computational intensity of covariate screen?

♦ Precursor to mechanistic model that included parent and 2 active metabolites, eased computational burden of covariate screening

Kambhampati et al ACoP 2017
What Mechanism Describes Abemaciclib PK and Active Metabolite Formation for E-R Analysis/Modeling?

Chigutsa et al ACoP 2017
Mechanistic PopPK Model Impact

- Described the disposition of parent and 2 active metabolites
- Useful as input to exposure-response analysis that could help to understand relative contribution of parent and metabolites to response endpoints
- Determination of covariate effects that could impact dose

Chigutsa et al ACoP 2017
Conundrum: Exposure-Response Static Analysis in MONARCH 2

![Graph showing progression-free survival over time for different groups with at-risk numbers and time in months.]

<table>
<thead>
<tr>
<th>Group</th>
<th>At Risk</th>
<th>Event</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY2835219 Q1</td>
<td>110</td>
<td>53</td>
<td>17.5</td>
</tr>
<tr>
<td>LY2835219 Q2</td>
<td>110</td>
<td>50</td>
<td>16.9</td>
</tr>
<tr>
<td>LY2835219 Q3</td>
<td>110</td>
<td>57</td>
<td>14.1</td>
</tr>
<tr>
<td>LY2835219 Q4</td>
<td>110</td>
<td>60</td>
<td>14.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>223</td>
<td>157</td>
<td>9.3</td>
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</table>
How did abemaciclib concentration affect tumor size change in MONARCH 2?
Positive Relationship between Exposure and Response (Tumor Shrinkage) in MONARCH 2

Starting dose and dose reductions
MONARCH 2 PopPK/PD Model Showed Higher Abemaciclib Concentrations Reduced Hazard of Progression

\[ \frac{d Haz}{dt} = HBASE \times e^{CFB \times THAZ - SLOPE \times CONC \times e^{-DECAY \times t}} \]
Positive Relationship Between Dose and Response (PFS) in MONARCH 2

- Confirmed appropriateness of starting dose and dose reductions used in registration study in light of the results from the static analysis
- Defined the efficacy portion of the therapeutic window, which could be used to evaluate scenarios such as impact of food effect and drug interactions
What was the relationship between abemaciclib exposure and neutropenia in MONARCH 2?
Exposure-Response Relationship for Neutrophil Progenitors in MONARCH 2

- Confirmed understanding of the frequency of this adverse event
- Defined an aspect of the safety side of the therapeutic window, which could be used to evaluate scenarios such as impact of food effect and drug interactions

\[
\text{Drug effect} = \theta_{\text{Fulvestrant}} + \theta_{\text{Abemaciclib}} \cdot (1 - MT) \cdot (\theta_{C_{\text{max,ss,total}}} \cdot \log(1 + C_{\text{max,ss,total}}))
\]
PBPK Model to Predict Effect of Unstudied Scenarios on Total Active Species PK Impacted Label

**Oral Dose 200mg**

- **Abemaciclib**
  - $V_{dss} = 8.93 \text{ L/Kg}$
  - $CL_{i.v.} = 24 \text{ L/h}$
  - $fm_{CYP3A4} = 0.89$

**Urine**

- $fe = 0.04$

- $fe = 0.04$
- $fm_{Non-CYP3A4} = 0.07$

**Other**

- $fm_{CYP3A4} = 0.48$
- $fm_{Non-CYP3A4} = 0.6$
- $fm_{Other} = 0.74$

**M20**

- CYP3A4 $fm = 0.32$
- CYP3A4 $fm = 0.09$
- Sulfation $fm = 0.26$

**M21**

**M18**

**Study design**

- Oral Dose 200mg
- $Fa = 0.91$
- $Fg = 0.74$
- $Fh = 0.69$

Posada et al ASCPT 2017
# Models Informed Abemaciclib Drug Development

<table>
<thead>
<tr>
<th></th>
<th>Pre-Clinical PK/PD</th>
<th>PopPK</th>
<th>PopPK/PD</th>
<th>PBPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous, twice daily dosing</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Identification/confirmation of a target systemic exposure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biomarker selection to demonstrate target engagement in patients</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariate evaluation, no dose adjustment needed for weight, etc.</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Acceptability of starting dose and dose adjustments for tolerability</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Understanding the risk for adverse events associated with changes in exposure</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Dose adjustment recommendations for drug interactions not studied</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Backups
Pred-corrected VPC of Empiric PK model

Kambhampati et al ACoP 2017
Diarrhea Time to Event Model

- Parameterized the observed slight reduction in exposure over time as the effect of diarrhea on PK
- Demonstrated that the risk of diarrhea was higher for doses ≥ 200 mg
- As precursor to mechanistic model that included parent and 2 active metabolites, eased computational burden of covariate screening

Kambhampati et al ACoP 2017
Neutrophil observations in MONARCH 2
Pred-corrected VPC of Mechanistic PK Model

Chigutsa et al ACoP 2017
VPC of Final Tumor Size Model with Dropout in MONARCH 2
Abemaciclib and Metabolite Observations and Predictions

200 mg abemaciclib

50 mg abemaciclib + clarithromycin

Posada et al ASCPT 2017
## CYP3A4 Inhibition Predictions

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>2.28 (2.10, 2.48)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>1.64 (1.57, 1.70)</td>
</tr>
<tr>
<td>M2</td>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>1.06 (1.04, 1.09)</td>
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<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>0.61 (0.57, 0.66)</td>
</tr>
<tr>
<td>M20</td>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>1.30 (1.25, 1.36)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>0.74 (0.71, 0.77)</td>
</tr>
<tr>
<td>M18</td>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>0.6 (0.55, 0.65)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ratio Geo mean (90%CI)</td>
<td>0.33 (0.29, 0.39)</td>
</tr>
<tr>
<td>Active Species</td>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; ratio Geo mean</td>
<td>1.63</td>
</tr>
</tbody>
</table>