Non-Clinical and Translational Safety for Early Development of Oncology Compounds

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Quantitative Translational Approaches in Oncology

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‘Oncology is different’

- Patients rather than healthy volunteers
- Heterogeneous population
- Poor prognosis, refractory disease, failed prior therapies
- Tolerance for side effects high
- Doses and duration of treatment are not limited by what was conducted pre-clinically
- Dosing to limit of tolerability (MTD)
- Dose limiting toxicities: nausea and vomiting, rash, fatigue, diarrhoea - understood and managed clinically

- Different perception of non-clinical safety in oncology given life-threatening nature of the disease
Development in Oncology: ‘efficacy’ and ‘tolerability’

- **Sphere**: Round objects such as baseballs experience a medium amount of drag.

- **Aerofoil**: The shape of an aircraft wing minimizes drag.

- **Square**: Flat, edged objects such as boxes experience a high amount of drag.

Aero Bridge increases downforce and reduces drag
Olaparib in combination with SoC

Preclinical data package: Standard monotherapy GLP (rodent and non-rodent)

Initial Phase 1 trial: Study 96 – Olaparib given in combination on a backbone of Carboplatin +/- Paciltaxel. 28 cohorts; 198 patients; 6 years; $14 million – tolerable schedule not determined

Opportunity: Exploit pre-clinical tools to better understand olaparib in combination-induced bone marrow toxicity to improve clinical outcome
Case Study 1: Olaparib in combination with SoC

- Used pre-clinical in vivo model (rat) to reproduce the clinical olaparib-carboplatin induced bone marrow toxicity
- Investigated mitigation strategies for bone marrow toxicity; assessed impact of schedules on efficacy
- Using PK/PD modelling to translate effects observed in rats to predictions for humans
- This information gave confidence to the Olaparib team to re-instate the phase 1 adjuvant breast cancer clinical trial of Olaparib given in combination with Carboplatin.

Claire Sadler
Preclinical Safety Input to Translational Decisions

- Setting preclinical potency criteria (in vitro/in vivo)
- Compound selection (ranking safety)

Preclinical Development

- Hazard/risk assessment
- Select safe starting dose & Schedule

Phase I/II

- Dose and Schedule Prioritization
- Combinations

Modelling can be applied to preclinical safety data across the pipeline
- Understanding of PK/PD relationships can be used to set potency criteria and select between compounds during discovery
- Identification of Therapeutic Index for in vivo findings to enable go/no-go to Candidate Selection / FTIM
- Safe Starting Dose Estimation (particularly important for combinations)
Bone marrow toxicity of a BRD4 inhibitor
BRD4 knockdown affects bone marrow

Recent experimental data in rodent models demonstrates that Brd4 knockdown inhibits the bone marrow progenitor cells, i.e. LSK Cells (Lin-Sca1+cKit+)

doi: 10.3978/j.issn.2218-676X.2013.10.05
Modelling Platelet Dynamics in Rat

Individual and population fits to platelet data in the Rat.

0.1 mg/kg QDx10

1 mg/kg BD (3 on, 4 off, 3 on)

1.5 mg/kg QDx10

Platelets (x10^9/L)

Time (hours)
Human predictions at clinically relevant doses & schedules

Rat Model

Human PK

Human / Rat in vitro potency

Human System Parameters

Projected Human PK

Simulation of human platelets over 28 day (672 hours) dosing period and washout period of inhibitor

At predicted QD dose of:
- low (56 mg) (A)
- mid (100 mg) and high (300 mg) QD doses (C & D).

Platelets (x10^9/L)

Time (hours)

Daily dose (mg)

Predicted percentage of grade 3/4 thrombocytopenia at nadir (%)

Platelet count at nadir (x10^9/L)

A

B

C

Dosing
- QD
- BD (3 days on 4 days off)
Comparison with dosing schedule optimization for Docetaxel

Fixed total cycle dose on different schedules (days-on/days-off)

Dose fractionation

1 on- 9 off
4 on- 24 off

Neutropenia Predictions

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0109892
Translating the bone marrow toxicity of combinations
Increase in combination therapies in Oncology

• When 2 agents demonstrate efficacy – possible next step is to combine them
  • May lead to increased efficacy
  • May combat resistance of targeted therapies
  • Go on top of SOC

• Novel: SoC (one dose/ schedule often fixed)

• Novel: Novel (wide open!)

• Many permutations of combinations
Case Study 2 - Safe Starting Dose: Novel+Novel combination

- In vitro: Hazard identification – synergistic bone marrow toxicity of combination

- In vivo: Risk assessment – bespoke in vivo combination study conducted to assess impact of agents dosed concurrently on bone marrow toxicity and peripheral blood.
Modelling the hematopoietic effects

Underlying Biology

Mathematical representation

Data Analysis: Model Fits

Reticulocytes (1x10^9/L)

Time (hr)

Vehicle

Low Dose of A

Mid Dose of A

High Dose of A

Low Dose of A+B

Mid Dose of A+B

High Dose of A+B

\[ MTT = \frac{4}{k_p} \]

\( k_p \) - slope C

Prol \( \rightarrow \) T1 \( \rightarrow \) T2 \( \rightarrow \) T3 \( \rightarrow \) Circ

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Example 2 - Safe Starting Dose: Novel+Novel combination

- **IMPACT:** Reduction in combination start dose
- Maximum effect on BM occurs after 2 cycles (not 1) therefore 2 cycles will be competed in the clinic before dose escalation
- Significant impact on bone marrow predicted in combination at 10mg of Cpd A – information used to assess degree of dose escalation
Predicting GI Toxicity from Rodent to Man
Prevalence of GI toxicity in oncology compounds

Oncology compounds often have on-target toxicity on rapidly dividing stem cells, even for targeted therapies (see table for AE’s for new therapies)

This is manifested as frequent bone marrow/hematological and GI tox in the clinic

Neutropenia has been shown to be predictable in severity and time course from preclinical using Friberg model (JCO, 2012) for a wide variety of compounds/mechanisms

Here we employ a similar approach for toxicity induced through damage to GI crypt stem cells

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence of diarrhea (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>55 (6% grade 3–5)</td>
<td>Shepherd et al. (2005)²</td>
</tr>
<tr>
<td></td>
<td>68 (12% grade 3–4)¹⁴</td>
<td>Herbst et al. (2005)³⁵</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>40–60 (8% grade 2)</td>
<td>Fukuoka et al. (2003)³</td>
</tr>
<tr>
<td></td>
<td>58 (3% grade 3–4)¹⁴</td>
<td>Herbst et al. (2004)³⁶</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>40 (10% grade 3)</td>
<td>Burrhis et al. (2005)²⁴</td>
</tr>
<tr>
<td></td>
<td>60 (13% grade 3–4)</td>
<td>Geyer et al. (2006)⁶⁷</td>
</tr>
<tr>
<td>HKI-272</td>
<td>84</td>
<td>Wong et al. (2006)¹⁹</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>33 (24% grade 2–3)</td>
<td>Escudier et al. (2005)¹⁰</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>20 (grade 2–3)</td>
<td>Motzer et al. (2006)¹¹</td>
</tr>
<tr>
<td>Imatinib</td>
<td>45</td>
<td>Demetri et al. (2002)¹⁴</td>
</tr>
<tr>
<td>Flavopiridol</td>
<td>50</td>
<td>Liu et al. (2004)¹⁵</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>32 (8% grade 3–4)</td>
<td>Fanucchi et al. (2003)³⁴</td>
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</table>

¹Drug used in combination with cytotoxic chemotherapy.

doi:10.1038/ncponc1087
Known GI effects of irinotecan

Patients

Diarrhea incidence for 125 mg/m²/wk for 4 weeks on and 2 weeks off

Hecht, Gastrointestinal toxicity of Irinotecan, Oncology, 1998

Rats

Gibson et al, J Gastroenterol Hepatol, 2003
Gl damage model built from literature

**Biological Understanding**

- **Villus**
- **Crypt**

**Model Structure**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rodent Model</th>
<th>Human Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem Cells/Crypt</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Stem cell doubling time</td>
<td>16 hrs</td>
<td>72 hrs</td>
</tr>
<tr>
<td>TADC doubling time</td>
<td>12 hrs</td>
<td>32 hrs</td>
</tr>
<tr>
<td>Shedding rate</td>
<td>0.45 /day</td>
<td>0.2 /day</td>
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<tr>
<td># of Transit compartments</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td># of Crypts feeding each villus</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
Data and predictions for the average score

**Pathology Score (N)**
1 - Minimal  
2 - Mild  
3 - Moderate  
4 - Marked  
5 - Severe
Prediction of clinical effects
Mechanistic model predicts well

Results for 125 mg/m²/wk for 4 weeks on and 2 weeks off

Hecht, Gastrointestinal toxicity of Irinotecan, Oncology, 1998
Clinical biopsy data can be predicted by model

Data lends support to the model that has both cell cycle arrest as well as cell killing.

Model predictions for extent of enterocyte loss in good agreement with villus shortening seen in biopsy data following chemotherapy.
Fits to Novel: Novel combination data

Drug X 1mg/kg days 1-3
Drug X 3mg/kg days 1-3
Drug X 10mg/kg days 1-7
Drug X 1mg/kg days 1-3; Drug Y 50mg/kg days 1-7
Drug X 3mg/kg days 1-3; Drug Y 50mg/kg days 1-6
Drug X 3mg/kg days 1-3; Drug Y 50mg/kg days 1-4
Drug X 10mg/kg days 1-3; Drug Y 50mg/kg days 1-5
Drug X 10mg/kg days 1-5; Drug Y 50mg/kg days 1-5
Preliminary predictions for human enterocytes

1 mg, 10 mg or 30 mg Drug X (additional therapy) once a day for 3 days followed by 4 days off –

Repeat regimen every week for 3 weeks
Summary

- Regulatory requirement for non-clinical safety work for oncology is limited
  - Single agent: Hazard ID, Escalation, SSD, Safety Pharmacology
  - Combination: minimal

- Opportunity to assess apply preclinical models with mathematical translation to improve chances of success:
  - Starting dose & escalation scheme
  - Risk of increased toxicity in combination therapies
  - Dosing schedule
  - Selection of combination partners

  - Predictive models needed for many endpoints (e.g. skin or immune)
  - Biomarkers with translational power (e.g. citrulline for GI toxicity, KIM1 for kidney)

- Need to challenge existing ways of thinking!
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<table>
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<th>Parameter</th>
<th>Estimate</th>
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<th>%IIV</th>
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<tr>
<td><strong>AZD5153 PK</strong></td>
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<td></td>
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<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>1.7</td>
<td>(fixed)</td>
<td>-</td>
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<tr>
<td>$V$ (L/kg)</td>
<td>0.39</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>$Cl$ (L/hr/kg)</td>
<td>0.15</td>
<td>(fixed)</td>
<td>-</td>
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<tr>
<td><strong>PD model</strong></td>
<td></td>
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<tr>
<td>$Circ_0$ (x10$^9$/L)</td>
<td>562.4</td>
<td>2.4</td>
<td>5.4</td>
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<tr>
<td>$MTT$ (h)</td>
<td>57.7</td>
<td>3.6</td>
<td>5x10$^{-4}$</td>
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<td>$\gamma$</td>
<td>0.5</td>
<td>10.3</td>
<td>0.1-</td>
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<td>$slope_{AZD5153}$ (1/(µmol/L))</td>
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