Dose Selection in Early Oncology Trials

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Oncology drug development has made substantial progress

More efficacious and safer treatment for longer-term use is necessary
Oncology dose finding paradigm has been changing

From identifying maximum tolerated dose (MTD) to optimizing dose regimen

- MTD may not be the optimal dose
- Maximum efficacy may be achieved below the MTD
- Optimal biologic dose to saturate target and block pathway
- Cancer may become chronic disease
- Long-term cumulative toxicity is important to address
Post marketing trials were required to optimize dose in recent oncology submissions

<table>
<thead>
<tr>
<th>Compound</th>
<th>M&amp;S summary</th>
<th>Post Marketing Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>PK and E-R modeling enabled dose escalation schemes</td>
<td>Dose escalation schemes approved</td>
</tr>
<tr>
<td>Trametinib</td>
<td>E-R relationship with biomarkers</td>
<td>No evident impact</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Exposure/Responder analysis</td>
<td>No evident impact</td>
</tr>
<tr>
<td>Trastuzamab emtansine</td>
<td>Narrow therapeutic window</td>
<td>Impact on dose uncertain, pending additional analyses</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>~80% dose reductions</td>
<td>Possibly new dose trial</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Dose modifications not supported</td>
<td>Develop 100mg formulation</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>ER suggests higher dose</td>
<td>Explore higher dose</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>No exposure-efficacy, yes with toxicity</td>
<td>Explore other regimens</td>
</tr>
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</table>
Dose optimization in oncology is challenging

- Narrow therapeutic index
- High variability of drug response
  - Heterogeneity of the disease and patients
  - Phase I patients not representing intended population
  - Heavily pre-treated and concomitant medications
- Development of drug resistance
- Complexity of the biology
- Linkage of biomarkers to clinical outcome can be difficult
- Limitation in study design due to severity of disease
- Urgency to deliver effective treatments to patients
M&S in early oncology trials can inform dose optimization

- Characterize exposure-response and therapeutic window
- Characterize time course of response
- Identify the biomarkers that correlate to pathway inhibition
- Leverage preclinical data
- Characterize inter-patient variability
- Inform both dose and schedule
Case Study 1: ABL001

Allosteric Bcr-Abl inhibitor for Chronic Myeloid Leukemia

ABL001
First in class allosteric inhibitor

Gleevec® (Imatinib)
Tasigna ® (Nilotinib)
Sprycel ® (Dasatinib)
Bosulif ® (Bosutinib)
Inclusig ® (Ponatinib)

Chromosomal Translocation

Biomarker of response
Molecular Response
Molecular response: primary efficacy endpoint

*Measurement of Bcr-Abl transcript*

- Assessed in peripheral blood by RT-PCR
- International scale: log reduction of transcript levels
  - >10%: failed MR
  - ≤10%: MR1
  - ≤0.1%: MR3 (MMR)
  - ≤0.01%: MR4 (CMR)
  - ≤0.0032%: MR4.5

**Diagram:**
- **Diagnosis**
- **Cytogenetics**
  - CCyR
  - MMR
  - CMR
  - ~5-6 log reduction

**Axes:**
- **Time**
- **Chronic myeloid leukemia (log10)**

**Legend:**
- MMR = major molecular response.
- CMR = complete molecular response.
- RT-PCR = reverse transcription polymerase chain reaction.
PKPD semi-physiological model

- Mimics leukemic cell maturation: Maturation time
- Reproduces disease progression: Immature cells turnover rate
- Accounts for existing resistance: Fraction of sensitive cells

\[ \text{MMT} = \frac{4}{ktr} \]

\[ (1 - frS) \cdot (ktr + grS) \]

\[ frS \cdot (ktr + grS) \]

\[ krs \cdot C(t) \]

- Describe BCR-ABL(%) kinetics
- Estimate concentration for stable disease
- Provide exposure target for dose and schedule optimization
Individual PD profiles

BCR-ABL (%)

Time (months of 28d)
Individual average concentration for stable disease vs. PK

- Population average concentration for stable disease = 1 ng/ml
- Individual values ranging from 0.07 to 61 ng/ml due to large variability on estimated individual disease progression

![Graphs showing concentration over time for different doses](image)
Clinical PKPD analysis results are consistent with preclinical data

- Required average concentration for stable disease = 1 ng/ml

- Individual values ranging from 0.07 to 61 ng/ml (0.014 to 122 nM)

- IC90 for pSTAT5 inhibition KCL-22 xenograft mice after PPB correction: 121 ng/mL (free: 11 nM)

- In vitro gIC50 KCL-22 cell line expressing WT BCR-ABL: 1 ng/mL (2.1 nM)
PK/PD analysis supported dose selection for Phase I expansion

- Clear advantage of 40 mg vs. 20 mg BID

<table>
<thead>
<tr>
<th>BID Dosing</th>
<th>Percent (95% CI) patients with at least 1 log 10 reduction</th>
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<tbody>
<tr>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td>Tx Duration</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>33% (24-42)</td>
</tr>
<tr>
<td>12 months</td>
<td>42% (32-52)</td>
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</tbody>
</table>
Case Study 2: WNT974

- WNT ligands activate the pathway
- Porcupine is required for WNT ligand formation
- WNT974 blocks Porcupine activity
- RNF43 and RSPO regulate Wnt pathway signaling

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PK modeling and ER analysis to support dose finding

- Exposure-response analysis identified a therapeutic window
- PK simulations found a dose yielding exposures within that window
- That dose has been selected as the recommended dose for expansion

<table>
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<th>Analysis</th>
<th>Objective</th>
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<tbody>
<tr>
<td>Population PK modeling</td>
<td>To characterize PK</td>
</tr>
<tr>
<td>ER analysis for biomarker</td>
<td>To explore and characterize the relationship of exposure vs. PD biomarker</td>
</tr>
<tr>
<td>Logistic regression for safety</td>
<td>To explore and characterize the relationship of exposure vs. AE</td>
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</table>
Population PK modeling

Single-dose

Dose - 5 mg

Dose - 30 mg

Repeat-dose

C1D15, 5 mg QD

C1D15, 30 mg QD

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Exposure-response analysis for PD biomarker and safety

EC₅₀ = 0.45 ng/mL (90% Prediction interval: 0.1 - 2.6)
Integrative analysis of PK, PD and safety data supported dose selection for Phase I expansion

<table>
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<tr>
<th>Endpoint</th>
<th>Criteria</th>
<th>Exposure threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>&gt;50% maximal inhibition with 95% probability</td>
<td>C_{\text{trough,ss}} &gt; 2.6 \text{ ng/mL}</td>
</tr>
<tr>
<td>AE</td>
<td>50% probability that &lt;25% patients have Gr\geq 2</td>
<td>C_{\text{max,ss}} &lt; 118 \text{ ng/mL}</td>
</tr>
</tbody>
</table>
Summary

- Prospective M&S in early oncology trials informs dose optimization
- M&S integrates data including PK, biomarker, efficacy and safety
- Models are continuously refined based on emerging data
- Greater need to apply quantitative methods to understand drug response
Thank you

• Varsha Iyer, Christophe Meille (ABL001)
• The individuals who worked to discover and develop these medicines
• The patients who participated in our clinical trials