FDA-AACR Public Workshop on

OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS

February 15, 2024, 8 a.m. – 5 p.m.
February 16, 2024, 8 a.m. – 1 p.m.
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Qi Liu, PhD
U.S. Food and Drug Administration
Quantitative Approaches to Select Dosages for Clinical Trials
Considering the Totality of Efficacy and Safety Data to Aide Registrational Trial Designs

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Office of Clinical Pharmacology
OTS/CDER/FDA

February 16, 2024
Opinions presented are those of the speaker and should not be construed to represent FDA’s views or policies.
Classic Dose-Finding for Oncologic Products

Dose Escalation

Time

Dose Level

Hallmarks:

- Few patients at each dosage
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety or data

*DLT = Dose-limiting toxicity
*MTD = Maximum tolerated dose
Possible Dosage Selection Strategy

Dose Escalation

Time

Dose Level

1

2

3

4

Dosage Optimization

Patients with Cancer

Dose Level 2

Dose Level 4

Select Dosage for Further Exploration

Evaluate Several Dosages
Holistic Approach

- Non-Clinical Data
- Dosage
- Activity
- Pharmacokinetics
- Safety, Tolerability
- Pharmacodynamics
How do we systematically evaluate all available nonclinical and clinical data?

Adapted from Dr. Youwei Bi update on MIDD program
PK = pharmacokinetics, PD = pharmacodynamics, PBPK = physiologically based pharmacokinetics, CiPA = comprehensive in vitro proarrhythmia assay
Model-Informed Drug Development

• Leverage a thorough understanding of the drug, a disease, and how a drug affects the human body, as well as how the body responds to the drug.

• Quantify information by developing mathematical models based on full use of all available data, from sources such as in vitro, nonclinical and clinical studies

• Apply this knowledge to address issues pertaining to drug development or clinical use.

Adapted from CDER Conversation with Dr. Madabushi
MIDD Can Facilitate Drug Development

• Predict concentrations at different moments in time, including doses and times not yet studied

• Test effects of covariates to identify differences in exposure in specific subpopulations

• Characterize dose- and exposure-response relationships at any stage of development

• Facilitate a thorough understanding of the therapeutic index

• Leverage published data to help understand drug class effects and inform trial design
Considering the Totality of Efficacy and Safety Data to Aide Registrational Trial Designs

1. Using Modeling-Based Approaches to Understand Dose- and Exposure-Response Relationships for Activity
   Dr. Jin Y. Jin

2. Using Pharmacokinetic-Pharmacodynamic Modeling and Simulation to Understand Dose and Exposure-Response Relationships for Adverse Reactions
   Dr. Scott Van Wart
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Using Modeling-Based Approaches to Understand Dose- and Exposure-Response Relationships for Activity

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Disclosure Information

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I have the following relevant financial relationships to disclose:
   Employee of:   Genentech, A Member of the Roche Group
   Stockholder in:   F. Hoffmann-La Roche

The views expressed in this presentation are my own and not reflective of Roche/Genentech
Outline

- Challenges and Opportunities for Dose Optimization in Oncology
  
  - Modeling-Based Approaches for Dose Selection (Registrational Trial)
    - mAb, solid tumor (*population PK & exposure target*)
    - TDB, heme (*QSP, RO-based exposure-response*)
    - SM, solid tumor (*biomarker PK/PD, exposure-response, clinical utility index*)
  
- Summary

Challenges and Opportunities for Dose Optimization in Oncology

- Therapeutic window
- Translation from preclinical-to-clinical and early-to-late clinical
- Phase 1 in patients – both challenge and opportunity
- Biomarkers (target, pathway, disease; circulating/biopsy; imaging/digital)
- PK confounding
- Immunogenicity (ADA)
- Confounding factors in patients
- Confounding of dose reduction, hold, missing
- Dose by body weight or flat dosing, administration route
- Combinations (PK DDI, efficacy, safety)
- Special population (pediatric, geriatric, renal/liver dysfunction, race/ethnicity)


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Case Example #1

Pertuzumab Dose Selection Based on Clinical PK and M&S

- Trough concentration >20 μg/mL target
  - Loading dose for Cycle 1 C_{trough} >20 μg/mL
- Dose to be in linear range of PK: 2~15 mg/kg
  - Saturate receptor-mediated clearance
  - Reduce clearance variability
- Low incidence of immunogenicity
- No effect of body weight on PK
- 840 mg loading dose followed by 420 mg Q3W maintain trough concentrations above the 20 μg/mL target in >90% of patients in all cycles based on M&S

**US Label**

**12.3 Pharmacokinetics**

Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of pertuzumab was reached after the first maintenance dose.

The population PK analysis suggested no PK differences based on age, gender, and ethnicity (Japanese vs. non-Japanese). Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.

Mosunetuzumab is a CD20/CD3 Bispecific Antibody for B-cell Malignancies:
- PK properties enable q3w dosing
- Does not require ex-vivo T-cell manipulation
- Off the shelf, readily available treatment

Mechanism of Action:
- Redirects T cells to engage and eliminate malignant B cells
- Potent tumor killing as single agent

Development Challenges:
- On-target acute toxicity for T-cell directing therapies
  - Cytokine release syndrome (CRS) occurs acutely following first doses and dissipates with time
- Challenges in dose finding
  - Complex target engagement
  - No simple PK target based on preclinical data
  - Phase I dose-response relationship was confounded by patients’ prior lines of therapies and on-board residual rituximab

Case Example #2
Mosunetuzumab Step-Up Dosing Strategy Supported by QSP Modeling

QSP Modeling to Describe IL6

Peripheral Blood

Bone Marrow

Spleen/Lymph Nodes

Tumor

Model-Predicted IL6 Following Fixed Dosing vs. Step-up Dosing Regimens

Clinical PD Consistent with Pharmacological Expectations:

Maximal IL6 elevation occurs after C1D1 dose even though PK continues to escalate with each repeat dosing

Case Example #2
Characterizing the Driver (RO) for Mosunetuzumab Clinical Response

Clinical dose-response un-informative: 1) small sample size, 2) confounded

Dose → PK → Receptor Occupancy → Clinical Response

RO%\(_{(t)}\)\text{mosun} = \frac{100 \cdot C_{\text{mosun}}(t)}{KD_{\text{mosun}} + C_{\text{mosun}}(t) + \frac{KD_{\text{mosun}}}{KD_{\text{rituxan}}} + C_{\text{rituxan}}(t)}
Case Example #2
Characterizing the Driver (RO) for Mosunetuzumab Clinical Response

Dose → PK → Receptor Occupancy → Clinical Response

RO-Based Exposure-Response in aNHL

Clinical dose-response un-informative: 1) small sample size, 2) confounded

Table 1. Recommended LUNSUMIO Dose and Schedule (21-Day Treatment Cycles)

<table>
<thead>
<tr>
<th>Day of Treatment</th>
<th>Dose of LUNSUMIO</th>
<th>Rate of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1 mg</td>
<td>Administer over a minimum of 4 hours.</td>
</tr>
<tr>
<td>Day 8</td>
<td>2 mg</td>
<td></td>
</tr>
<tr>
<td>Day 15</td>
<td>60 mg</td>
<td></td>
</tr>
<tr>
<td>Cycle 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>60 mg</td>
<td>Administer over 2 hours if infusions from Cycle 1 were well-tolerated.</td>
</tr>
<tr>
<td>Cycles 3+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>30 mg</td>
<td></td>
</tr>
</tbody>
</table>

The PI3K/AKT pathway is central for cancer cell growth and survival

Ipatasertib (GDC-0068) is a potent, oral, ATP-competitive AKT inhibitor

Optimal biological dose selected for Phase 2 based on target specific biomarker response and PK/PD
Ipatasertib Phase 3 Dose Selection: Account for Confounding of Dose Reduction


DI Model 1: Prob(DI≥1) vs. Dose

Logistic regression fit line
Observed probability of DI≥1 with SE bars

DI Model 2: DI distribution in DI<1 population

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Case Example #3
Ipatasertib Phase 3 Dose Selection: Exposure-Response Analyses

Exposure-Efficacy: radiographic PFS

Exposure-Safety: Gr2+ Diarrhea

Dose-rPFS projections from Cox regression model of exposure-rPFS coupled with dose intensity model

Dose-safety projections from logistic regression model of exposure-safety coupled with dose intensity model (Gr2+ diarrhea*)

*Similar analyses conducted for: Gr3+ diarrhea, Gr2+ rash, Gr3+ rash

Benefit-risk analysis via exposure-response and clinical utility index (CUI) approaches indicated that Ipatasertib 400 mg QD has the highest probability of achieving the minimal Product Profile (PP) with best benefit/risk balance, which was thus selected for Phase 3.
Summary

- Dose optimization strategy should be seamlessly integrated into clinical development plan across life-cycle (Dosing CDP)
  - Multiplicative considerations: molecule mode of action, indication specific efficacy need, patient tolerance/quality-of-life, CMC feasibility, cost and speed
  - Cohesive cross-functional partnership is essential

- Modeling-based approaches play an integral role in drug development and dose selection
  - Effectively integrate totality of evidence (PK, biomarker, efficacy, safety)
  - Leverage knowledge/data across molecules
  - Provide mechanistic insight and dosing projections
  - Guide study design and early go/no-go decision making potential
  - Wide range of modeling approaches are available (empirical, mechanistic, artificial intelligence).
    Selection of approach should be science/data driven and fit-for-purpose.
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Genentech Clin Pharm Team
Project Teams
Internal Collaborators
External Collaborators
Investigators
Patients
Using Pharmacokinetic-Pharmacodynamic Modeling and Simulation to Understand Dose and Exposure-Response Relationships for Adverse Reactions

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Disclosure Information

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I am the founder and Chief Scientific Officer of Enhanced Pharmacodynamics, LLC (ePD)

ePD consults with or has received research funding from various companies including: Adagio, Arcturus, AstraZeneca, Biogen, Boston Biomedical, Daiichi Sankyo, EMD Serono, Eleevar Therapeutics, Eli Lilly, Enlaza Therapeutics, Enliven Therapeutics, EUSA, Genentech, Genmab, Glenmark, GSK, Halozyme, ICPD, Ionis Pharmaceuticals, Ironwood Pharmaceuticals, Jazz Therapeutics, Leyden Labs, Merck, Nektar Therapeutics, Nurix Therapeutics, Nutcracker Therapeutics, Oncoceutics, Praxis Therapeutics, PharmaEssentia, Roche, Sarepta Therapeutics, Seagen, Servier, Takeda, Teva, Tubulis, UCB Pharma, Veradermics, Via Nova, Windtree Therapeutics, and Zogenix.
Exposure-response PK-PD analyses for safety are a critical component of model-based drug development

- Used to provide decision-support criteria initially to guide dose escalation and later optimization during Phase 1 of development and to identify the RP2D
- Safety AE and efficacy PK-PD models can be linked together to determine realistic patient dropout rates when performing simulations of ORR, OS and PFS
- Can be used to understand potential impact of combination therapy or prophylactic use of other concomitant medications (e.g., GCSF) to counteract side effects

This presentation will provide a few examples of how we have been asked to use PK-PD modeling and simulation for safety AE to help support dose regimen selection for clinical trials
Combining Logistic Regression Analysis of Safety AE Data with PK-PD Model for Tumor Growth to Optimize Dose
Review Totality of Safety AE Data

- Review totality of treatment-emergent AE (TEAE) classification data across clinical trials, and if possible by Body System / Organ Class or Preferred Term

<table>
<thead>
<tr>
<th>AE Classification</th>
<th>All Clinical Studies Combined (N=1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Events</td>
</tr>
<tr>
<td>All TEAE (any grade)</td>
<td>1623</td>
</tr>
<tr>
<td>All TEAE of Grade 3+</td>
<td>324</td>
</tr>
<tr>
<td>TEAE of Blood and Lymphatic System Disorders (any grade)</td>
<td>412</td>
</tr>
<tr>
<td>TEAE of Blood and Lymphatic System Disorders (Grade 3+)</td>
<td>212</td>
</tr>
<tr>
<td>TEAE of Thrombocytopenia (any grade)</td>
<td>512</td>
</tr>
<tr>
<td>TEAE of Grade 3+ Thrombocytopenia</td>
<td>112</td>
</tr>
<tr>
<td>TEAE of Neutropenia (any grade)</td>
<td>217</td>
</tr>
<tr>
<td>TEAE of Grade 3+ Neutropenia</td>
<td>84</td>
</tr>
</tbody>
</table>

Note: Rate is the percentage of the population with at least one TEAE of the given category
Exploratory PK-PD Analysis for Safety AE Data

- Boxplots can be used to show dose- and exposure-response relationships
- Examining different PK exposure metrics can help determine if there is signal and which metric might be most predictive prior to running the logistic regression.
PK-PD Models for Efficacy and Safety AE

PK-PD Model for TGI

Logistic Regression PK-PD Model for Safety AE

\[ p = \frac{1}{1 + e^{-\left(\beta_0 + \sum \beta_i \cdot X_i\right)}} \]

Predicted probability of Grade 3+ TEAE plotted vs. observed incidence rate within each AUC quantile
PK-PD Simulations to Optimize Dose

<table>
<thead>
<tr>
<th>Dose (mg QD)</th>
<th>% of Simulated Subjects with Grade 3+ TEAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>5.2%</td>
</tr>
<tr>
<td>100</td>
<td>7.1%</td>
</tr>
<tr>
<td>150</td>
<td>12.4%</td>
</tr>
<tr>
<td>200</td>
<td>23.0%</td>
</tr>
<tr>
<td>250</td>
<td>36.5%</td>
</tr>
<tr>
<td>300</td>
<td>48.1%</td>
</tr>
<tr>
<td>350</td>
<td>62.9%</td>
</tr>
<tr>
<td>400</td>
<td>71.4%</td>
</tr>
<tr>
<td>450</td>
<td>75.5%</td>
</tr>
<tr>
<td>500</td>
<td>88.2%</td>
</tr>
</tbody>
</table>

Note: Median and 90% PI shown for 500 virtual subjects. Dashed green line denotes 30% decrease in sum of diameters relative to baseline (solid black line).
Example 2:

Longitudinal PK-PD Models for Myelosuppression to Inform Dose Regimen and Clinical Trial Design
Comparison of Myelosuppression for Vyxeos® vs. Standard 7+3 Therapy

- Vyxeos® (CPX-351) is a liposomal encapsulation of daunorubicin (44 mg/m²) and cytarabine (100 mg/m²) approved for newly diagnosed therapy-related AML or AML with myelodysplasia-related changes in adults and pediatric (aged ≥ 1 year) patients.

- Population PK and PK-PD models were developed to characterize the impact of daunorubicin and cytarabine on ANC and platelets to compare liposomal Vyxeos® to standard 7+3 therapy.
PK-PD Models for Myelosuppression for Vyxeos® vs. Standard 7+3 Therapy


Application of PK-PD Models for Myelosuppression to an ADC

Assumed no systemic deconjugation of payload e.g. $[\text{CAB}] = [\text{TAB}]$

ADC dosed Q3W x 3
Simulations for Impact of Dose Interval and GCSF on ADC Dosing Regimen

ADC dosed Q3W x 3

ADC dosed Q4W x 3

ADC dosed Q4W x 3, with 6 mg SC Pegfilgrastim 2 weeks after each ADC dose

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Example 3:

Predicting the Impact of Combination Therapy on Myelosuppression to Select Starting Dose for Clinical Trials
Impact of Combination Vyxeos® and Venetoclax on Myelosuppression

- Venetoclax (B-cell lymphoma 2 inhibitor) is approved in combination with low-dose cytarabine for patients with AML who are ineligible for IC

- Semi-mechanistic PK-PD models for both ANC and platelet counts were developed to characterize the myelosuppressive effects of Vyxeos® and venetoclax monotherapy
  - Vyxeos® pop PK model was used along with mean PD data for first induction cycle from 3 clinical studies conducted in AML patients
  - Venetoclax pop PK model and mean PD data were obtained from literature

- Goal was to predict the safety profile and to recommend starting dose for low-intensity therapy of Vyxeos® plus venetoclax
Impact of Combination Vyxeos® and Venetoclax on Myelosuppression


PK-PD Model Fitting for CPX-351

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ANC</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final Estimate</td>
<td>RSE (%)</td>
</tr>
<tr>
<td>Circ₀ (10⁹/L)</td>
<td>4.45</td>
<td>8.9</td>
</tr>
<tr>
<td>MTT (h)</td>
<td>66.6</td>
<td>5.0</td>
</tr>
<tr>
<td>γ</td>
<td>0.0278</td>
<td>8.1</td>
</tr>
<tr>
<td>I_max</td>
<td>1 fixed</td>
<td>0.313</td>
</tr>
<tr>
<td>IC₅₀ for CPX-351 (µM)</td>
<td>295</td>
<td>8.96</td>
</tr>
<tr>
<td>IC₅₀ for Venetoclax (µM)</td>
<td>120</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Each unit of CPX-351 contains 1 mg cytarabine and 0.44 mg daunomycin. ANC, absolute neutrophil count.

Simulations to Select Starting Vyxeos® Dose for Phase 1b Study

20 units/m² Vyxeos® on Days 1 and 3; 400 mg Venetoclax QD until Day 21

- Simulations used to determine starting dose for LiT of Vyxeos®/venetoclax for Ph 1b study in newly diagnosed AML patients unfit for IC
- Targeted ≥ 50% of patients to recover above Grade 4 at end of 28-day cycle

These examples illustrate how PK-PD modeling and simulation can be used to support dose optimization and inform the design of clinical trials.

A wide range of PK-PD modeling approaches can be used to characterize safety AE data and the same data can in fact be modeled multiple ways (e.g., categorical vs. continuous time-course models).

Innovative approaches leveraging literature data or other published PK-PD models can provide tremendous value during drug development to help improve patient outcomes.
SESSION 3A: CONSIDERING THE TOTALITY OF EFFICACY AND SAFETY DATA TO AIDE REGISTRATIONAL TRIAL DESIGNS

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