Dose-finding of Small Molecule Oncology Drugs

May 18-19, 2015

Washington Court Hotel,
Washington DC
Day 1: Welcome and Workshop Objectives

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Session I: Small Molecule Characterization

Pharmacology Matters: Adapting the Paradigm of Small Molecule Oncology Drug Development
Natalie Simpson, PhD
Pharmacology/Toxicology Reviewer, Division of Hematology Oncology Toxicology (DHOT), OHOP, OND, CDER, FDA

Is It Safe: Understanding the Performance of Nonclinical Safety Assessment Models in Predicting Human Outcomes?
Thomas W. Jones, PhD
Chief Scientific Officer, Toxicology and Pathology, Eli Lilly & Co.

Nonclinical to Clinical Correlation of Adverse Effects of Kinase Inhibitors
Richard Brennan, PhD, DABT
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Pharmacology Matters: Adapting the paradigm of small molecule oncology drug development

Natalie E. Simpson, Ph.D.
DHOT/OHOP/OND/CDER/FDA
Disclaimer

- The opinions expressed in this presentation are those of the presenter and do not necessarily reflect official support or endorsement by the Food and Drug Administration.
Introduction

- It is difficult to optimize therapeutic doses for targeted therapies like kinase inhibitors using the traditional paradigm for cytotoxic drugs:
  - Exposure response relationships are rarely defined resulting in frequent dose reductions due to dose limiting toxicities (DLTs)
  - Inter-patient variability is not adequately evaluated during early clinical development
  - Sponsors have to conduct additional dose optimization studies post-marketing

- What steps can we take to address this problem and improve dose optimization for kinase inhibitors?
  - Multi-disciplinary approach

- The goals of this session are to identify the key “best practices” in the nonclinical evaluation of a compound (selectivity, pharmacology, secondary pharmacology and toxicology) and integration of this information during dose optimization.
Challenge in Finding the “Right” Dose for the “Right” Patient

- Ponatinib and nilotinib - favorable risk-benefit profile, but also a history labeling changes:
  - Early clinical trials and animal toxicology studies did not predict toxicity - thromboembolism and vascular occlusion adverse events.
  - Toxicities are delayed and cumulative.
- Industry has made changes and has valuable insight to improve dose optimization based on such examples.
Was There Other Information That Could Have Helped Predict Toxicity?

- Clinical experience and pharmacology data suggest that DLTs may be related to the promiscuous activity of kinase inhibitors.
  - Kinase inhibitors target different mutations; often = less selectivity.
- Drugs with a common target have common toxicity, but likely not only explanation for vascular events with ponatinib and nilotinib:
  - There is increased risk for vascular occlusive events with ponatinib and nilotinib compared to other ABL kinase inhibitors.
  - Secondary pharmacology data also suggest differential targeting among ABL kinase inhibitors for kinases involved in vascular maintenance (e.g., inflammatory responses, angiogenesis pathways).
Hierarchical Clustering of Grade 3-4 Cardiovascular Events

- Preferred term (PT) of Grade 3-4 Cardiovascular Treatment Emergent Adverse Events (AEs) Grouped by Type of Event
- Unsupervised Hierarchical Clustering of AEs by Drug Performed for Selected Kinase Inhibitors (ABL, VEGFR, EGFR)
Broad Target Selectivity for Many FDA-approved Kinase Inhibitors

1 µM kinase inhibitor profiled against 300 kinases in a biochemical enzymatic assay

Uitdehaag et. al, PLOS ONE (2014)
Hierarchical Clustering of Kinase Inhibitors by % Inhibition of Kinases Known to Affect Endothelial Survival/Function and Vascular Maintenance

- Drugs with high inhibitory activity for kinases involved in vascular maintenance/function
- Drugs with little effect

Differential targeting within cluster

Low % inhibition

High
Goal 1: Discuss Safety Evaluation of Kinase Inhibitors Using Pharmacology/Toxicology

The current paradigms recommended per ICH S9 guidance:

- Prior to Phase 1 for advanced oncology indications:
  - Primary pharmacology studies to support mechanism of action/anti-tumor activity
  - Toxicology studies (typically 28-days duration)

- Prior to Phase 3:
  - Longer duration toxicology studies (3-months)

- How can secondary pharmacology be useful in addition to the current paradigm?
Goal 2: Identify “Best Practices” in Industry for the Evaluation of Lead Compounds

• “Best practices” for selectivity and potency (in vitro):
  - What types of studies are conducted (direct binding/functional assays)?
  - Presentation and interpretation of data for target selectivity and potency (methods, structure-activity relationships, threshold for positive hit, % inhibition, IC$_{50}$)?

• “Best practices” for correlation of animal and human toxicities/predictivity of DLTs:
  - Species selection?
  - Limitations of animal studies to identify DLTs for non-cytotoxic therapies?
  - Correlations/predictivity dependent on target organs and class effects?

• Open dialogue to define value/utility of studies (binding, biochemical enzyme activity studies, cell-based studies, etc.) in dose optimization and possible standardization.
Goal 3: Discuss De-Risking Strategies for Molecularly Targeted Anticancer Drugs

• How can pharmacology data help to fill gaps left by toxicology studies?
  ➢ Is there information that is not typically submitted to the Agency that could be used in safety assessment?
  ➢ Understanding of in vivo activity; encompassing differences in kinase pathways among species and context-specific function in different tissues/organs.
  ➢ Use of computational modeling (systems biology) to handle massive amounts of data.

• Safe vs. management
Goals 4 and 5: Discuss Approaches to Integrating Information Gleaned from the Nonclinical Evaluation into the Design of Phase 1 Clinical Trials and the Role of the Nonclinical Team During the Development Process

• Overall goal is to increase safety and efficiency in clinical trials with the prospective use of available nonclinical data.
  - Use of PK/PD and PK/toxicity relationships, selection of dose and dosing schedule?
  - Iterative process as nonclinical and clinical (PK/activity/toxicity) data become available?

• Role of the nonclinical teams during the development process?
  - Clinical trial design?
  - Attribution of toxicities to study drug?
  - Clinical toxicity management and clinical dose optimization?
“Wish List”

• Learn in this workshop the “best practices” for better dose optimization for targeted small molecule oncology drugs.

• Take home message that “pharmacology matters”:
  ➢ A thorough understanding of the drug target(s) and activity should help to maximize their therapeutic benefit and minimize risk.
  ➢ Most reliable and biologically relevant kinase inhibition data (encompassing the entire kinome, description of methods, standardized platforms) will be used to make cross-drug comparisons for risk assessment.
  ➢ Relationship of secondary pharmacology data to safety, not just efficacy will also be described in regulatory submissions.

• Correlation of clinical adverse events with kinase inhibitory profiles (pharmacology) and clinical exposure (pharmacometric) data will be used in addition to current methods to better predict toxicity and find the right dose for the right patient.
Goals for the morning session

- Discuss safety evaluation of kinase inhibitors using pharmacology/toxicology
- Identify “best practices” in industry for the evaluation of lead compounds
- Discuss de-risking strategies for molecularly targeted anticancer drugs
- Discuss approaches to integrating information gleaned from the nonclinical evaluation into the design of Phase 1 clinical trials
- Discuss the role of industry nonclinical teams during the development process
Back-up Slide – Regulatory applications of “off-target” pharmacology data

- Off-target activity is often used to make regulatory decisions for other less severe indications (Papoian T et al., Nature Reviews Drug Discovery):
  - PPARgamma agonist - more extensive cardiac monitoring in humans/ request for longer duration tox studies with more in depth analysis of target tissues
  - hERG antagonist; 5-HT2B (serotonin) receptor agonists - more extensive cardiac monitoring in humans
  - NMDA receptor antagonists – focused animal studies to detect neurotoxicity
  - ER antagonist – PMR requirement for juvenile toxicology study (oncology indication)
Nonclinical to clinical correlation in adverse effects of kinase inhibitors

Richard J. Brennan
Preclinical Safety
Sanofi, Waltham, MA

Dose-finding of Small Molecule Oncology Drugs
May 18-19, 2015, Washington Court Hotel, Washington, DC
Agenda

- Clinical application of kinase inhibition – a brief history

- Kinase inhibitor safety in practice and prediction
  - The Good
    - Direct preclinical correlations
  - The Bad
    - Some translatable observations
  - The Ugly
    - Lack of Predictivity

- Kinase inhibitor promiscuity and prediction of multi-factorial AE
Approval History of Small Molecule Kinase Inhibitors (Ki) (USFDA Approvals)

Data from “USFDA approved protein kinase inhibitors compiled by Robert Roskoski Jr.”
http://www.brimr.org/PKI/PKIs.htm

* As of Feb 13
KI Clinical Adverse Effects

● Most Ki Indications to date in oncology
  ● Higher tolerance for adverse effects than non life-threatening and chronic disease

● Some common AE are target-related “class effects”
  ● EGFR and acneiform rash
  ● VEGFR and hypertension

● AE profile and severity dependent on kinase profile and relative potency
  ● Imatinib, nilotinib, dasatinib (Bcr-Abl, PDGFR – targeted for CML)
    • Myelosuppression severity related to relative affinity for c-Kit
    • Edema Imatinib (55%) > dasatinib (18%) > nilotinib (<4%)
      • Related to PDGFR potency
    • Pleural effusion with dasatinib (14-30%), rare for imatinib or nilotinib
      • Possibly related to Src family activity, multi-factorial
Preclinically-predicted AE’s

- **Dermatotoxicity (EGFR)**
  - Acneiform rash, xerosis, alopecia, facial hypertrichosis
  - Mouse, rat, dog

Brown et al, 2008
Toxicologic Pathology, 36: 410-419

Hyperkeratosis, acanthosis
Pyogranulomatous inflammation
Preclinically-predicted AE’s

- **Developmental & reproductive toxicity**
  - Critical role of cell proliferation/apoptosis, vascularization, differentiation pathways
  - 32 of 33 marketed Ki have pregnancy category C or D indicating positive risk to animal (C) or human (D) fetus
  - **Imatinib experience**
    - 150 conceptions reported by exposed males
      - 148 normal deliveries
    - 167 women exposed during organogenesis period of pregnancy
      - 128 normal deliveries
      - 24 spontaneous abortions
      - 15 births with abnormalities (skeletal, vascular, organ formation, low birth weight)

- Generally well predicted in rat and rabbit
Preclinically-predicted AE’s

- **GI Toxicity**
  - Severe diarrhea
  - Perforations

- **Hematopoetic Toxicity, lymphopenia**
  - ABL, BTK, c-met, MEK, JAK, VEGFR, mTOR
  - Rat, dog, non-human primates all sensitive
  - Oversensitivity with some agents (possibly dose-related)
AE’s with Some Preclinical Correlates

- **Ocular toxicity**
  - Retinal Vein Occlusion (MEK)
    - Replicated in rabbit, not seen in rat or dog
  - Other serious effects on posterior segment are rare
    - Hemmorhage, retinopathy
    - Axitinib, trametinib, imatinib, vemurafinib
  - Conjunctivitis (EGFR)
    - Corneal thinning in rat and dog, lens opacity in dog
  - Visual disturbance with crizotinib (Alk, Met, Ros1)
    - Subjective reporting
    - Electroretinography changes (light-dark adaptation) in rat study

- **Other preclinical effects**
  - Lens opacity
    - Seen with mTORi in rat, ibrutinib (Btk, Lck, Lyn) in dog
  - Keratitis, exudates, retrobulbar hemmorhage with nilotinib
    - Rat only
AE’s with Some Preclinical Correlates

- **Cardiovascular AE**
  - QT prolongation, arrhythmia
    - Ion channel effects e.g. nilotinib/hERG predictable
  - Hypertension, bleeding, LVEF, heart failure
    - VEGFR
    - Ventricular hypertrophy and pulmonary artery wall thickening in rats treated with VEGFRi neonatally
    - Left and right ventricular function decreased 30-40% in dogs (sunitinib) not seen in rats
  - Cardiomyopathy, LVEF, cardiac failure
    - MEK
    - LVEF changes in rat
  - Congestive heart failure, LV dysfunction
    - Abl (Bcr-Abl)
    - LV dysfunction and cardiomyocyte loss in mice
AE’s with Some Preclinical Correlates

- **Hypothyroidism**
  - VEGFR, PDGFR, RET, BRAF
  - Thyroid highly vascularized, VEGF dependent
  - Regression of thyroid capillaries (68%) and increased TSH (19x) in VEGFRi-treated mice (21 days)
  - Reversible on Ki withdrawal
Poorly-Predicted AEs

- **Hepatotoxicity**
  - 16 marketed KI require liver function monitoring
  - Clinical evidence for dasatinib

- **Multiple mechanisms**
  - Reactive metabolites
    - Erlotinib
  - CYP inhibition
    - Lapatinib, pazopanib,
  - UDPGT1A9 inhibition (acetaminophen detoxification)
    - Imatinib, sunitinib
  - UGT1A1 inhibition (bilirubin clearance)
    - Regorafinib, erlotinib, nilotinib, sorafenib, pazopanib
    - Gilbert’s Syndrome (lapatinib, pazopanib)
  - Transporter inhibition
    - Pazopanib & simvastatin
  - Genetic Factors
    - HLA variants & lapatinib

Of 26 total marketed SM Ki

![Venn diagram showing overlap between Human, Rat, and Dog (11 tested) arising from mechanisms and genetic factors.](image-url)
Poorly-Predicted AEs

- Renal toxicity
  - VEGFR, EGFR, mTOR

Of 26 total marketed SM Ki
*Keller, D.A., Brennan, R.J. and Leach, K.L., 2015*
Poorly-Predicted AEs

- Interstitial lung disease (ILD), non-infectious pneumonitis
  - ILD rare but life-threatening
  - EGFR, MEK, ALK, mTOR, broad-spectrum Ki
  - Human-specific risk factors
    - Smoking, pulmonary fibrosis, Japanese ancestry
  - Complex diagnosis including CT imaging
  - Occasional lung lesions in rat

- Reversible posterior leukoencephalopathy
  - VEGF
  - Not detected in preclinical models
Target-Related AE
Targeted Therapies?

178 Ki (broad target classes) vs. 300 recombinant kinases (>500 known kinases)

**Imatinib**
Bcr-Abl targeted, Abl1, Abl2, PDGFR, cKit, cFms, DDR2, Lck

**Sunitinib**
VEGFR1-targeted, PDGFR, Flt1, cKit, Flt3, DRAK1, cFms, BIKE, PHKG1

Kinase inhibition heat map of 113 small molecule kinase inhibitors assayed for micronuclei and a 290 Ambit panel

Machine learning (Random Forest, SVM) identified 21 kinases predictive of MNT with 85% accuracy (68% sensitivity, 91% specificity)

Some kinases have known involvement in cell cycle or chromosome stability, several do not
Bioinformatics and Systems Biology Approaches to Predicting AE

Curated AE (78 distinct terms)
20 KI
266 distinct targets (<10uM)

Conclusions

- Small molecule kinase inhibitors are a clinically important and effective addition to the oncology pharmaceutical toolbox.

- Adverse effects are less severe and more manageable than standard chemotherapy.
  - Some life-threatening reactions
  - Many AE not well predicted by standard preclinical safety profiling
  - AE profiles may not be acceptable for non-oncology indications

- Many AE can be understood and predicted based on target biology.

- Ki are promiscuous and many targets have poorly profiled function and associated risk.

- Computational and modeling approaches may be useful.
  - Comprehensive, well-annotated datasets of clinical and preclinical AE and target activities required
  - Pre-competitive data sharing initiatives needed
Panel Discussion
Session I: Small Molecule Characterization

Moderators:
Todd Palmby, PhD
FDA
Donna Dambach, VMD, PhD
Genentech

Panelists:
• William Kluwe, PhD, Novartis Institutes of Biomedical Research
• Richard Brennan, PhD, Sanofi
• Thomas Jones, PhD, Eli Lilly & Co.
• Eric Rubin, MD, Merck Research Laboratories
• Kourosh Parivar, M.Pharm, Pfizer
• José Pinheiro, PhD, Janssen
• Alice Shaw, MD, PhD, Massachusetts General Hospital
• Pasi Jänne, MD, PhD, Dana Farber Cancer Institute
Goals for Session 1

1. To discuss the evaluation of a compound, including selectivity and potency, primary and secondary pharmacology and toxicology.

2. To discuss the selection of lead compounds, the correlation of animal and human toxicities and predictivity of toxicology studies in identifying clinically relevant DLTs.

3. To discuss de-risking strategies for molecularly targeted anticancer drugs.
Goals for Session 1

4. To discuss approaches to integrating information gleaned from the nonclinical evaluation into the design of Phase 1 clinical trials.

5. To discuss the role of industry nonclinical teams during the development process of anticancer drugs including clinical trial design, attribution of toxicities to study drugs, clinical toxicity management and clinical dose optimization.
Panel Discussion
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• José Pinheiro, PhD, Janssen
• Alice Shaw, MD, PhD, Massachusetts General Hospital
• Pasi Jänne, MD, PhD, Dana Farber Cancer Institute
Session II:
Design of Dose-finding Studies

Dose Selection for Small Molecule Oncology Drugs: Present State and Future Considerations
Nitin Mehrotra, PhD
Team Leader, Division of Pharmacometrics, Office of Clinical Pharmacology (OCOP), OTS, CDER, FDA

Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example
Dinesh De Alwis, PhD
Executive Director, Late Stage, Quantitative Pharmacology and Pharmacometrics
Merck Research Labs

Innovations in Dose-finding Clinical Trial Designs
Laura Fernandes, PhD
Mathematical Statistician, Division of Biostatistics V (DBV), OB, OTS, CDER, FDA
Dose Selection for Small Molecule Oncology Drugs: Present State and Future Considerations

Nitin Mehrotra
Team Leader, Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/FDA

The contents and ideas of this presentation are mine and do not necessarily reflect any position of the Government or the Food and Drug Administration.
Emerging Trends in Oncology

PMR/PMC to address dose optimization

Evaluation & approval of doses lower than MTD

2011
Vandetanib
Crizotinib
Omacetaxine
Cabozantinib
Ponatinib
Radium-223 Dichloride
Idelalisib
Lenvatinib
Panobinostat

2012
2013
2014
2015

Enzalutamide
Trametinib
Ibrutinib

2012
Dabrafenib
Afatinib
Idelalisib

2014

Slide adapted from Anshu Marathe’s presentation at American Conference on Pharmacometrics, ACoP 2014
Current State: Dose Selection in Oncology

- ‘MTD paradigm’ is still commonly used for dose selection
- Target inhibition, biomarker and early clinical data not critically evaluated for dose selection
- Phase 2 trials rarely evaluate more than one dose or dosing regimens
- Characterization of PK/PD and exposure-response in early clinical trials is not consistently across INDs
Answering the Key Question: “Do we have the right dose?”

Adequate dose ranging trials

Model based dose selection

Disease models: Tumor response-outcome relationship

Exposure-response (ER) for efficacy & safety

Increased Recognition of ‘Dose Selection’ in Oncology
Idelalisib
for Relapsed CLL, Follicular B-cell NHL & Small Lymphocytic Lymphoma

Approval of Dose Lower than MTD

Clinical pharmacology review by Drs. Stacy Shord & Dhananjay Marathe:
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205858Orig1s000ClinPharmR.pdf
Background

- **Idelalisib**: Inhibits ATP binding to the catalytic domain of phosphatidylinositol 3-kinase delta (PI3Kδ)
  - EC$_{90}$: 125 ng/mL
  - Half life: 8.2 h

- Dose ranging trial evaluated QD and BID dosing regimens upto 350 mg BID (MTD not reached)

- Proposed dosing regimen: 150 mg BID

**Is 150 mg BID the right dose?**
PK Justification for 150 mg BID Dosing Regimen

EC₉₀, 125 ng/mL
PK Simulations to Support the 150 mg BID Dosing Regimen

Cumu. Distri. of $C_{\tau_a}$ in a population

$EC_{90}$ (125)

$C_{\tau_a}$ (ng/mL)

50 mg

100 mg

150 mg

200 mg

350 mg

37%

11%

3%
ER Based Justification for 150 mg BID Dosing Regimen

Range of exposures with 150 mg BID

Q1 to Q4: Exposure quartiles
Axitinib
for Advanced Renal Cell Carcinoma

Utilizing Dose Individualization in Drug Development

Clinical pharmacology review by Drs. Sarah Schrieber, Nitin Mehrotra & Rosane Charlab Orbach:
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000ClinPharmR.pdf
Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202324s002lbl.pdf
Background

- **Axitinib**: Inhibitor of VEGFR 1,2,3
- **Dosing regimen**: Start at 5 mg BID, increase to 7 mg BID to a maximum of 10 mg BID based on tolerability
- 5 mg BID is the MTD
- Titration scheme evaluated in clinical trials
- **AEs**: Hypertension, proteinuria, diarrhea and fatigue

**Is the proposed titration based dosing regimen appropriate?**
Exposure Dependent Increase in Hypertension and Proteinuria

**Similar relationships for Fatigue and Diarrhea**
Dose Titration Based on Tolerability Produces Similar Exposures Across Doses

Prior to Dose Titration

At 5 mg BID Dose Level

N=131
N=31
N=13

Highest BID Dose Received

After Dose Titration

Highest BID Dose Received

BSV in Clearance ~ 60% CV
Examples of Recent Trial Designs (Learn-Apply)

**Fixed dosing changed to Body weight (BW) based dosing**

Phase 2 trial for Drug X: Higher discontinuation/dose reductions in lower BW compared to higher BW patients

PK: Low BW $\rightarrow$ High exposure

Fixed dose changed to body weight based dose:
- Low BW: Lower dose
- High BW: Higher dose

**Model-based dose selection for Phase 3**

PK/PD model for Drug Y developed from Phase 2 data

Efficacy dependent on baseline PD biomarker level

PK/PD simulations conducted to derive phase 3 doses not directly evaluated in Phase 2:
- Dosing based on baseline PD biomarker was proposed
## Evidence Generation: Our Experience in Context of Dose Selection

<table>
<thead>
<tr>
<th></th>
<th>We are here</th>
<th>This is the target</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Scenario 1</td>
<td>Scenario 2</td>
</tr>
<tr>
<td>MTD Determination</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Modeling and simulation to design trials</td>
<td></td>
<td>✓</td>
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<tr>
<td>Assessing efficacy of lower doses /alternate regimens</td>
<td></td>
<td>✓</td>
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<tr>
<td>Exposure-response (efficacy and safety) based dose justification: IND stage</td>
<td></td>
<td>✓</td>
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<tr>
<td>Covariate based dosing in registration trials</td>
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<td>✓</td>
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<tr>
<td>Exposure-response (efficacy and safety) based dose justification: NDA/BLA</td>
<td>✓</td>
<td>✓</td>
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*Scenarios 1 to 4 are hypothetical scenarios for comparison purpose only*
Dose Selection: Future Considerations “Wish List”

- Dose ranging trials
- Pharmacometric exposure-response models
  - ER based justification for dose selection in INDs/NDA/BLAs
  - Innovative quantitative analysis to support dose selection (multivariate analysis, modeling time course of AEs, etc.)
- Disease models
- Utilizing integrated dose-exposure-response modeling and simulation for dose selection and trial design
- Building ‘dose individualization’ concept as part of clinical development program
Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example

Dinesh de Alwis, PhD

Merck/MRL/PPDM, Quantitative Pharmacology and Pharmacometrics
Dinesh De Alwis, Ph.D.

I have the following financial relationships to disclose:

- I am an Employee and Stockholder of Merck & Co, Inc
- I will not discuss off label use in my presentation.
Oncology Early Phase Dose Selection needs Significant Improvement

MTD is not always the approved dose

- Dose $\leq \frac{1}{2}$ MTD: 25 (32%)
- Dose slightly below MTD: 23 (30%)
- Dose $\geq$ MTD: 29 (38%)

Roughly 2/3rd (48/77) of the compounds are approved at doses lower than MTD
Roughly 1/3rd (25/77) are approved at less than MTD/2

Manuscript submitted
## Assessing Toxicities for Non-cytotoxic Therapies

### 201 phase 1 trials: 119 cytotoxic trials and 82 non-cytotoxic trials

### Finding MTD for non-cytotoxic drugs in Ph1 is likely to be challenging

<table>
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<tr>
<th>DLTs actually identified</th>
<th>Cytotoxic drugs</th>
<th>Non-cytotoxic drugs</th>
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<tbody>
<tr>
<td></td>
<td>106/119 (89%)</td>
<td>43/82 (52%)</td>
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### Categories

<table>
<thead>
<tr>
<th></th>
<th>Cytotoxic drugs</th>
<th>Non-cytotoxic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectively quantifiable</td>
<td>67 (56%)</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Clinically gradable by physician</td>
<td>12 (10%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Reported by patient</td>
<td>15 (13%)</td>
<td>10 (12%)</td>
</tr>
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Only 50% Ph. I trials identify MTD

Of this 50%, only 30% (15% of original set) report objectively quantifiable and clinical toxicities

**Objectively quantifiable**: biological anomalies (renal, liver, hematological function, level of serum CPK, metabolic parameters) or ventricular dysfunction.

**Clinically gradable by the physician** with some difficulties, such as skin reactions, mucositis and diarrhea.

**Subjective toxicities**: reported by patients and could not be objectively measured by the physician. This category includes pain, fatigue and multiple combined side effects.

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Evidence that, for Targeted Therapies, Doses Reaching MTD Increase Toxicity Without Necessarily Improving Response in Phase I Onc. Patients

Doses approaching MTD led to more patients off trial due to toxicity

MTD does not necessarily improve response

Normalization to combine data from different trials:
- low-dose: ≤25% MTD of the trial
- High-dose: ≥75% MTD of the trial
- Medium-dose: 25-75%

24 trials treating 683 patients between Oct, 2004 - Jun, 2008, at MD Anderson Cancer Center
Impact Phase I Design and aid in Go/No GO, Use of Pharmacological Model Based Phase I Design

All attention on finding MTD! 3+3, CRM, mCRM, TITE-CRM, accelerated titration, ...

What about efficacious dose? Deserves more attention

Part A: Dose Escalation
1 pt cohorts → 3 pt cohorts (with 3 pt expansion if DLT)
Dose escalation to MTD

Part B: Dose Confirmation
(2-3 arm study exploring MED, BED and MTD dose range / regimen)

MTD
BED = Biologically Effective dose
MED = Minimally Effective Dose

Toxicity, PK, or dose trigger to convert to 3 pt cohorts
Expand to three cohorts to explore dose and regimen (n=12-15)
Oncology Drug Development: Phase 1b/2

- **Design of Ph 1b/2**
  - Randomized Studies
  - Evaluate more than one dose
  - Look at surrogate end points to make early go / no go decisions based on safety, efficacy, and, where possible, biology (quantitative PD assay or grade of AE, etc.)
  - Look for factors contributing to individualized response: demographics or tumor genetics, etc
  - Establish POC
    - Has drug reached the site of action?
    - Has POM been established?
    - Has efficacy been established in the targeted patient population (e.g. better than SOC)?
    - Has an adequate therapeutic range been established?
MTD not an option for TGFbeta Targeted Agent due to preclinical cardiotox: predict efficacious clinical dose of LY2157299 using PKPD

Results from preclinical work:
• Understood PD required for tumor growth delay
• Understood dose range (160-300mg total daily dose) likely to produce clinical efficacy (and informed use of 2 wk on/2 off regimen)

Several cell lines used to try to understand GBM (Calu6, MX1, …)

LY2157299: Best Overall Response in the Clinic at Predicted BED*

1. Predicted efficacious dose range from translational models
2. Found efficacy in those ranges in the clinic without going to MTD
3. MTD was not an option here because of preclinical cardiotox

Now in Phase II/III


*BED: Biologically Efficacious Dose
**Crizotinib**: Preclinical data helped identify relevant target, and inhibition level of that target needed for TGI*

Dual inhibitor of the c-Met and ALK receptor tyrosine kinases

1. ALK inhibition is Predictive of TGI*

2. Significant MET inhibition does not always inhibit tumor growth

3. Efficacy (TGI) is driven by ALK inhibition, Not MET Inhibition

* TGI: Tumor Growth Inhibition

Crizotinib Mechanistic understanding
→ determined MTD had adequate target inhibition
→ selected patients with ALK positive tumors

1. Mechanistic understanding of PKPD from preclinical

2. Predicted human at 250 mg BID would have ~75% inhibition in Alk activity
   (enough for preclinical TGI)
   → Predicted effective dose = MTD

3. Clinical trial designed using 82 ALK positive patients

4. Clinical result: 72% PFS at 6 months

NEJM, 2010; 363: 1693
Another end point

The Concept Behind **Change in Tumor Size** ("CTS")

Easier to distinguish outcomes (more information)

Harder to distinguish outcomes (less information)

Five example outcomes we should be able to leverage to inform decisions: classification obscures and amplifies outcome differences

Preserving **continuous** information at the patient level leads to **more information per subject**

("increased statistical efficiency")
The Concept Behind Change in Tumor Size ("CTS")

Preserving continuous information at the patient level leads to more information per subject ("increased statistical efficiency")

Sample size required for a continuous endpoint (CTS) can be 44% to 64% less than needed for a dichotomous endpoint (RR) for a randomized 2-arm study

Based on Lavin, 1981: Not a new concept but the revival of an old one
How can we use change in tumor size?

Enables earlier assessment of response (week 9, 18, 27 scans).

• POC: Demonstrate exposure-response
  - Drug should **not** exhibit tumor growth at the minimum
  - Ability to select sub populations that respond due to increased power compared to RR (initial tumor size, biomarker status, ECOG)
  - Ability to identify optimal dose and indications
    • Increases confidence to decide which doses or indications to pursue (which arms to expand to more subjects)
  - Link to survival and PFS
Critique of tumor size endpoint
Ignores new lesions, dropouts & death

- Challenge: Mixing continuous tumor sizes and event data

- Proposed approach: Probabilistic (Bayesian) method to estimate probability of response (PR)
  - Integrates information about new lesions, dropouts & death with continuous tumor sizes

- Simulations re-running past trials showed PR gives same power with 25-50% fewer subjects in phase 1 and 2 trials, or substantially more power with the same number of subjects
Conclusions

- Paradigm Change for Oncology Dose finding Required
  - MTD is sometimes useful (and sometimes possible)

- Need to use all available information (Toxicity, Preclinical, Clinical PK/PD information to help design Phase IB studies to explore BED.

- Tumor size change aligns with the therapeutic goal of anti-cancer treatment
  - Use of continuous endpoints including tumor size is going to be critical for designing efficient, rapid studies

- Key objective is to determine the most efficacious* dose/regimen and indication, and the most responsive patients.

*(or at least the most [rapidly] register able)
Acknowledgements

- Kapil Mayawala
- Jeff Sachs
- Satvik Gadamsetty
- Junghoon Lee
- Peter Kang
- Eric Rubin
Innovations in Dose-Finding Trial Designs

Laura L. Fernandes, PhD
Statistical Reviewer, DBV
Office of Biostatistics, OTS, CDER, FDA

FDA-AACR: Dose-Finding of Small Molecule Oncology Drugs Workshop
18 May 2015
Disclaimer

The views expressed in this presentation are those of the speaker and do not necessarily represent the policy of either the Food and Drug Administration or the Department of Health and Human Services.

I have no financial disclosures to report.
Outline

Introduction
  Dose finding phase I trials in oncology

Current Methods
  Phase I Trials
  Statistical Model-Based Approaches

Future Direction
  Current State
  Innovations for the Future
Outline

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Future Direction
  Current State
  Innovations for the Future
Dose finding trials in oncology

Before initiating a clinical dose finding trial:

- Developed a well characterized small molecule
- Completed non-clinical PK/PD modeling
- Completed non-clinical trials in animals
Three main goals

- Goal 1 - Obtain a good estimate of maximum tolerable dose (MTD)
- Goal 2 - Safety - limit number of dose limiting toxicities (DLTs)
- Goal 3 - Treat patients at biologically active dose levels, gain experience at the recommended dose level

Traditionally the focus has been on goals 1 and 2 but recent clinical trials in oncology attempt to achieve goal 3 by demonstrating an objective response rate (ORR).
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Traditionally the focus has been on goals 1 and 2 but recent clinical trials in oncology attempt to achieve goal 3 by demonstrating an objective response rate (ORR).
Typical Phase I trials in oncology

- Small trials $N \sim 30$
- Non-randomized and sequential in nature
- Patients receive a fixed dose from a pre-specified set of dose levels
- Utilize fixed dosing cycles of 21 or 28 days
- Could be Algorithm or Model-based designs
Algorithm Based Designs

- Traditional A+B Design
- “3+3” Design
- Up and Down Design

Properties

- Ad-hoc, widely used, easy to understand and execute
- Rigid, not flexible
- No mathematical framework
- Inefficient “short term memory” – uses data only from the recent cohorts
- Likely to treat patients at low, ineffective doses, large uncertainty about the chosen MTD
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Model Based Approaches

Usually have three components:

- A statistical model describing the dose toxicity relationship
- A set of priors incorporating additional information
- A framework to draw inference using the available data to make assignments for the next patient
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Examples of Model Based Approaches

- Continual Reassessment Method (CRM)
- Modified version of CRM - TITE-CRM
- Accelerated Titration Design
- Escalation With Overdose Control (EWOC)
- Modified toxicity posterior intervals (mTPI).
Properties of Model-Based Approaches

In comparison to algorithm based methods:

- MTD estimation is precise and accurate
- “learns” from information gained at early time points
- A mathematical framework allows to draw inference
- Incurs fewer cases of dose limiting toxicities
- Less likely to treat patients at toxic doses and more likely to treat patients at MTD
Recent Examples - Ceritinib approved in 2014*

- ALK-Rearranged NonSmall-Cell Lung Cancer
- a dose-escalation phase, followed by an expansion phase
- dose escalation guided by a two-parameter Bayesian logistic-regression model
- patients given the dose on day 1, followed by 3 days of PK monitoring
- patients continued to receive daily dosing for the remainder of 21-day cycle
- starting dose used was 50mg

*Alice T. Shaw et. al. NEJM, 2014
Ceritinib Example contd.

- priors set on the two parameters, in the Bayesian model, based on non-clinical data
- only the response from the first cycle used to fit the model

<table>
<thead>
<tr>
<th>Table: Number of patients (n) at each of the dose levels (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level</td>
</tr>
<tr>
<td>n</td>
</tr>
</tbody>
</table>

- 750mg was declared as the MTD and used in the expansion phase
- 74% of the patients required at least one dose reduction or interruption due to adverse reactions (ARs)
Ceritinib Example contd.

- priors set on the two parameters, in the Bayesian model, based on non-clinical data
- only the response from the first cycle used to fit the model

Table: Number of patients (n) at each of the dose levels (mg)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
<th>750</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>12</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

- 750mg was declared as the MTD and used in the expansion phase
- 74% of the patients required at least one dose reduction or interruption due to adverse reactions (ARs)
Current Gaps

- not using all the information from each patient and all patients in the trial
- incorporation of the non-clinical, historical data in the trial design
- lack of monitoring patients for longer durations
- monitoring long term safety, delayed toxicities
- mimic longer duration of drug usage beyond the 21 or 28-day cycle
- dose reductions in later stages of clinical testing/trials
Wishlist for the Future - 1

Incorporate data from multiple cycles from the same patient; use of repeated measures

- Possible methods to incorporate this data include -
  - intra-patient dose escalation model, Simon (1997)
  - extensions to the CRM for repeated measures, Legedza and Ibrahim (2000)
  - cumulative hazard model for schedules, Zhang and Braun (2013)

Long term safety and late onset or delayed toxicities

- cumulative hazard model for schedules, Zhang and Braun (2013)
- extensions to the TITE-CRM model for repeated measures
Wishlist for the Future Future - 2

- How do we study dose combinations
  - Two agent dose finding trials, Thall (2003)
- How do we incorporate data from non-clinical and other clinical studies
  - Priors on the parameters could reflect this information
- Use of priors in the Bayesian model
  - Criteria for use of non-informative priors, historical data or pre-clinical data
  - Use of modeling and simulations to mimic reality
- How to think beyond the 28/21-day cycle?
  - Unlike chemotherapy, small molecule drugs are administered on a continuous/daily long term basis
Wishlist for the Future - 3

- Ease of fitting Bayesian models
  - Elicitation of priors
  - Evaluation of prior performance
  - Validation of software for computing the integrals - posterior density

- Evaluating safety and efficacy
  - Capturing the response rate and safety

- Need statisticians to rise up to the challenge
  - Be sensitive to change, paradigm shift
  - Collaborate with multiple teams and disciplines
References

- Braun T; The bivariate continual reassessment method: extending the CRM to phase I trials of two competing outcomes. Controlled Clinical Trials 2002; 23(3):240–256.
- Legedza, A. and Ibrahim, J; Longitudinal design for phase I clinical trials using the continual reassessment method; Controlled Clinical Trials 2000; 21:574 -588.
- Mandrekar SJ, Qin R and Sargent DJ; Model-based phase I designs incorporating toxicity and efficacy for single and dual agent drug combinations: Methods and challenges; Stats in Medicine 2010; 29(10):1077–1083.
- Thall PF, Cook JD; Dose-finding based on efficacy/toxicity trade-offs. Biometrics 2004; 60(3):684–693.
- Zhang J and Braun T; A phase I Bayesian adaptive design to simultaneously optimize dose and schedule assignments both between and within patients. JASA 2013; 108 892-901.
Session II: Design of Dose-finding Studies

Best Practices of Adaptive Dose-finding Studies
Stuart Bailey, PhD
Global Head, Early Clinical Biostatistics, Novartis Oncology

Best Practices of Adaptive Dose-finding Studies II
José Pinheiro, PhD
Senior Director, Janssen

Pharmacometrics in Industry
Amit Roy, PhD
Group Leader, Clinical Pharmacology & Pharmacometrics, Bristol Myers Squibb
Best practices of adaptive dose-finding studies

Stuart Bailey, D.Phil., Global Head – Early Clinical Biostatistics, Novartis Oncology

Dose-finding of Small Molecule Oncology Drugs
May 18-19, 2015. Washington DC
Disclosure Information

FDA-AACR Dose-finding of Small Molecule Oncology Drugs
Stuart Bailey

I have the following financial relationships to disclose:
Stockholder in: Novartis AG, Novartis Pharmaceuticals
Employee of: Novartis Institutes for Biomedical Research Inc.

- and -

I will not discuss off label use and/or investigational use in my presentation.
Best practices for adaptive dose-finding

Incorporate historical information

- Understand your drug and the pathway/mechanism
  - Don’t assume “more is better” - MTD may not be required

- Design must maintain protection of patient safety
  - Quantify risk and uncertainty

- Incorporate preclinical/historical information
  - Preclinical toxicology (safety signals), pharmacology (target exposures, DDI), mechanism of action (biomarkers), patient selection
  - Assess consistency of patient data with preclinical information

- Communication is key – simple, common language
  - Internal (statisticians with non-statisticians)
  - External (regulators, investigators)
DLT-based dose-finding

*MTD paradigm*

Phase I dose escalation

Dose + DLT algorithm = MTD
DLT-based dose-finding

*MTD then RP2D paradigm*

Phase I dose escalation

- **Dose** + **DLT (BLRM)** = **MTD**
- **Escalation** + **Dose Expansion ≤ MTD** = **RP2D**
Best practices for adaptive dose-finding

Bayesian model-based approaches

- Bayesian approach offers formal method to quantify our knowledge and assess risk to future patients
  - Allows us to incorporate historical data
  - Bayesian Logistic Regression Model (Neuenschwander et al., 2008)

- “Appropriate” models allow us to share information between doses – efficient use of data
  - Parameterization is important!

- Flexibility to include additional patients, study multiple dose levels, re-escalate if data supports

- Explore “unplanned” doses; change schedules/formulations
  - Need some assumptions of the impact of changes!
Statisticians need to communicate complex ideas in a simple and effective way

- Use graphics whenever possible and know your audience
  - Statistician: “Median of prior distribution for logistic parameters from preclinical data with 95% credible interval”
  - Clinician: “Estimated dose-DLT relationship based on animal data and our uncertainty”
Best practices for adaptive dose-finding

*Historical information – communicating uncertainty*

- What sort of curves are ‘possible’ based on our prior?
- Plotting a random sample helps demonstrate that preclinical information could lead to many realities.
What sort of curves are ‘possible’ based on our prior?

Plotting a random sample helps demonstrate that preclinical information could lead to many realities.
Best practices for adaptive dose-finding

*Historical information – communicating uncertainty*

- Animation showing relationship between curves and $P(DLT)$ at a given dose
  - Helps to demonstrate concept of overdose risk
Escalation with Overdose Control

*Babb et al. 1998 – DLT risk assessment*
Escalation with Overdose Control

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Escalation with Overdose Control

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Escalation with Overdose Control

Babb et al. 1998 – DLT risk assessment

![Graph showing probability density distribution with critical values indicating acceptable and excessive toxicity](image-url)
Escalation with Overdose Control

*Babb et al. 1998 – DLT risk assessment*

![Graph showing probability density and toxicity levels](image)
Dose decisions  
*Identifying potential dose levels*

- Graphical summaries used to support dose escalation decisions
  - Model DOES NOT make recommendations
  - All other study data is used to select from identified doses

![Graphical summaries used to support dose escalation decisions](image_url)
Recommended dose every time

Assimilating information

Safety (AE, SAE, DLT)

Efficacy

Tolerability (Interruptions, Reductions, RDI)

Pharmacodynamics (pathway biomarkers)

Pharmacokinetics (AUC, Cmax, Ctrough, t_{1/2}, etc)

Recommended Dose
Best practices - Summary

Applying adaptive study designs

- Ensure availability of data
  - Safety, activity, “Real-time” PK, PD
  - Review acute and chronic treatment effects

- Design should allow data to impact on-study decisions
  - Dose levels, schedule/formulation changes
  - Adaptive patient recruitment, sub-population expansions

- Expansion should not be restricted to a single dose-level

- Strong relationship between clinical team members
  - Medical Lead, Statistician, Pharmacologist, Biomarker Specialist, (and the preclinical team)
  - Experienced investigators
Review of all study data

Changing data into decisions

<table>
<thead>
<tr>
<th>Patient</th>
<th>T_max</th>
<th>C_max</th>
<th>AUC_{24h}</th>
<th>AUC_{96h}</th>
<th>AUC_{inf}</th>
<th>T_{1/2}</th>
<th>CL/F</th>
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<td>3070</td>
<td>84.6</td>
<td>543</td>
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<tr>
<td>#2</td>
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<td>55.8</td>
<td>263</td>
<td>527</td>
<td>808</td>
<td>75.2</td>
<td>2060</td>
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<tr>
<td>#3</td>
<td>8.00</td>
<td>36.3</td>
<td>690</td>
<td>2070</td>
<td>2440</td>
<td>31.1</td>
<td>682</td>
</tr>
<tr>
<td>Mean</td>
<td>5.33</td>
<td>88.7</td>
<td>777</td>
<td>1590</td>
<td>2110</td>
<td>63.6</td>
<td>1100</td>
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<td>SD</td>
<td>3.06</td>
<td>74.5</td>
<td>562</td>
<td>918</td>
<td>1170</td>
<td>28.6</td>
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<td>Min</td>
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<td>1380</td>
<td>2160</td>
<td>3070</td>
<td>84.6</td>
<td>2060</td>
</tr>
<tr>
<td>CV%</td>
<td>57.3</td>
<td>84.0</td>
<td>72</td>
<td>58</td>
<td>56</td>
<td>44.9</td>
<td>76.7</td>
</tr>
</tbody>
</table>

Delta QTcF > 20 msec

Change from Baseline of QTcF (msec) versus observed conc

Review of all study data

Changing data into decisions
Paradigm shift
Clinically-driven, statistically supported decisions

Historical Data (prior info)

Trial Data 0/3, 0/3, 1/3, ...

Model based dose-DLT relationship

DLT rates $p_1, p_2, ..., p_{MTD}, ...$ (uncertainty!)

Potential “safe” Doses

Decisions Dose, schedule formulation, patients

Review of other clinical data (PK, PD, activity, late cycle AEs, tolerability)

Model

Inference

Decision/Policy

Responsible: Statistician (risk)
Informing: Clinician (Prior, DLT)

Responsible: Clinician
Informing: Statistician, pharmacologist, biomarker specialist,
Bayesian model based dose finding

A single agent case study
BLRM in practice – Study set up

- Developing new compound – first in human study
  - IV, once weekly, advanced solid tumors

- Available preclinical data
  - Rat – Human equiv. STD10 = 20 mg/m\(^2\), 1/10 STD10 = 2 mg/m\(^2\)
  - Dog – Human equiv. HNSTD = 28 mg/m\(^2\), 1/6 HNSTD = 4.5 mg/m\(^2\)

- Start dose for study = 2 mg/m\(^2\) weekly

- Our available knowledge centers around 2 species
  - Want to include this information into the prior dose-response prediction
  - Additionally want to allow for the fact that humans may be more tolerant of the drug

- Provisional doses (mg/kg): 2, 4, 7, 11, 15, 20, 26, 32

- Maximum 100% increase of dose
  - Max. 50% increase if DLT occurs or if 2 or more grade ≥ 2 treatment-related AE are seen
**BLRM in practice – Dosing decisions**


- No DLT seen at 2, 4, 8, 16 mg/m²
  - Dose doubled for first three escalation steps
  - Next dose recommended as 22 mg/m²
    - Can’t always dose double, depends on available information

- 1 DLT seen at 22 mg/m² in 4 patients
  - Additional cohort recruited – 0 DLT in another 5 patients
  - Escalate to 28 mg/m² – 0 DLT seen in 5 patients

- Next cohort was 40 mg/m²
  - 2 DLT seen in 7 patients
    - 3+3 would stop the trial here and declare MTD to be 28 mg/m²
    - BLRM allowed recruitment of additional patients to 40 mg/m² if team agreed
    - Lower doses were expanded and 40 mg/m² was reassessed
      - no additional DLT seen in 6 patients
BLRM in practice – Study outcome

<table>
<thead>
<tr>
<th>Dose</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>22</th>
<th>28</th>
<th>40</th>
<th>54</th>
<th>70</th>
<th>70 EXP</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>8</td>
<td>16</td>
<td>18</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>DLT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

- Additional patients recruited at dose below 70 mg/m² to investigate potential for specific AEs (possible class effect of compound)
  - DLT data from these additional patients was utilized by the model

- Clinical review recommended 70 mg/m² as phase II dose
  - Supported by BLRM – low risk of “excessive toxicity”
  - **Remember 3+3 would have recommended 28 mg/m²**
    - Would we trust 3+3 with limited data?
  - Dose declared is 2.5 times higher than 3+3 MTD but with stronger evidence
  - Subsequently 70 mg/m² shown to be both safe and had activity in patients
AUY922 Proof of Concept Declaration

Summary of information

✓ Biomarker

HSP70 upregulation

✓ Client Downregulation

HER2 downregulation in HER2+ pts (Zr PET)

✓ CT Partial Response

CT: PR

✓ PET Partial Response

FDG-PET (PMR)

✓ PET Response

Dose-dependent PMR by PET, 7/15 pts dosed with 70 mg/m²
BLRM in practice

Case-study summary

- Used all available historical data to deal with preclinical variability
  - Both dog and rat data integrated into the prior

- Moved through the dose range into region of the recommended dose in a controlled manner
  - Steps suggested by statistical inference and decisions supported by clinical expertise and all available clinical information

- Able to include information from all patients to make more appropriate decisions
  - 2 DLT may be acceptable for expansion if the denominator is >6
Best practices for adaptive dose-finding

Summary

- Statisticians with strong communication skills
  - Able to explain difficult concepts effectively (e.g., risk/uncertainty)
  - Support ongoing data interpretation (not over-interpretation)

- Prioritize your questions
  - Not everything needs to be (or can be) answered in a single study

- Communicate!!
  - Be explicit about the decisions that can be taken in the study
  - Help regulators to understand the process to adapt

- Ensure data is available
  - Without the data we are reliant on DLT and MTD paradigm
Recommended dose every time

Broader development context

- **Recommended Dose**
  - Safety (AE, SAE, DLT)
  - Tolerability (Interruptions, Reductions, RDI)
  - Pharmacokinetics (AUC, Cmax, Ctrough, t1/2, etc)
  - Pharmacodynamics (pathway biomarkers)
  - PK-PD modeling
  - Dose-Exposure-Response
  - Efficacy

- **Subpopulation** (e.g., NGS, Pediatric, ethnic sensitivity)
- **PK-QTc** Hepatic impairment
- **Quality of Life**
- **Cost of goods**
- **Food-effect, Formulation or schedule changes**

- **Subpopulation** (e.g., NGS, Pediatric, ethnic sensitivity)

- **Best Practices in Adaptive Dose-Finding**
  - Stuart Bailey | FDA-AACR | May 18, 2015
Best practices for adaptive dose-finding

Summary

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  - Without the data we are reliant on DLT and MTD paradigm
Thank you for your attention

Any questions?
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- Matthew Whiley
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- Daniel Lorand
References


Improving Dose Selection for Confirmatory Studies with Model-Based Approaches

José Pinheiro, Janssen R&D

Joint work with Frank Bretz and Björn Bornkamp, Novartis AG

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Employee of: Johnson & Johnson

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Motivation: need to improve dose selection

Pairwise comparisons vs. modeling

MCP-Mod dose finding approach

Conclusions and further thoughts
Improper understanding of dose response (efficacy and safety), resulting in inadequate dose selection for confirmatory programs remains a critical problem in drug development, including Oncology

- Need to repeat Phase 2 studies
- Delays or denial of regulatory approval
- Post-approval changes in dose, often reductions (leading to loss of revenue)

Some common reasons:
- Phase 2 studies designed as mini-Phase 3 studies, using pairwise comparisons to control for dose selection
- Few doses evaluated, often with similar efficacy (plateau of dose response profile), covering relatively small dose range

Recognized by regulators and industry, but difficult to change
Dose finding Phase 2 studies

- Two main goals
  - Proof-of-concept (PoC): identify evidence of dose response (DR) signal on efficacy
  - Dose selection: which dose(s) to take to confirmatory program – e.g., minimum effective dose (MED), ED90 (dose producing 90% of maximum possible improvement over placebo)

- Design and analysis strategies fall into two broad classes
  - Pairwise comparisons between doses and placebo (accounting for multiplicity) with dose selection driven by hypothesis testing
  - Modeling of DR relationship(s), with dose selection driven by model-based estimation (e.g., dose corresponding to minimum clinically relevant effect)
Pairwise comparisons vs. modeling on MED estimation

- Either D2, D3 or any dose in-between could be estimated as MED
- Modeling is more flexible, but requires additional assumptions
Model-based dose selection is not simple

- Shape of dose/exposure response profile typically unknown at design time – risky to pre-specify it
- Pre-specified profile shape will have a substantial impact on the final dose estimate and may not agree with observed data
- Model selection using observed data needs to account for the inherent uncertainty
  - Useful to have a unified approach combining the advantages of dose response signal testing and modeling
  - MCP-Mod: A structured approach to model-based design and analysis of Phase II dose finding studies under model uncertainty
MCP-Mod: A unified dose finding approach

General design considerations
- Determination of suitable study population, endpoints, etc.

Set of candidate models
- Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests
- Optimized for candidate dose-response shapes

Design evaluations
- Dose determination and sample size calculation to achieve targeted performance characteristics

Trial Design Stage

Trial conduct

Trial Analysis Stage

MCP step
- Assessment of dose-response signal using contrast tests
- Model selection (or model averaging) out of the set of significant models

Mod step
- Dose-response and target dose estimation based on selected model(s)

$p < \alpha$?
MCP-Mod (cont.)

- Combines MCP and modeling for model-based dose selection (and DR estimation) under model uncertainty

- Can be used to test DR signal (MCP step) and for DR estimation (Mod step): model selection or model averaging

- Intended for Phase II, but extension available for confirmatory studies (closed-test MCP-Mod)

- Can handle most common types of responses: continuous, binary, count, time-to-event, etc.

- Number of doses/dose range:
  - Minimum: 2 active doses (for the MCP-step), 3 active doses (Mod step)
  - Recommendation: 4-7 active doses, >10-fold dose range
Example: dose finding in respiratory disease

- Phase II study for NME in chronic respiratory disease
- Primary goal: select dose for Phase III program
- Doses: 0.25, 0.5, 1, and 2 mg, placebo, active control (AC)
- Primary endpoint: change from baseline in trough FEV1 at Day 14 (24 hr post-dose)
- Target dose: min dose with clinically relevant improvement over of placebo of 120 mL (MED); not worse than AC
Subgroup of Japanese patients

- Global development of compound (US, EU & Japan): Approximately one quarter of the patients in the study are Japanese

- Potential differences in dose-response and target dose estimate (i.e., MED) between Japanese and non-Japanese patients to be explored as supportive analyses
Candidate dose-response shapes
Types of analyses

● Three types of DR analysis implemented:
  ● Pooled: all patients, irrespective of race and ethnicity
  ● Japanese: only subgroup of Japanese patients
  ● Non-Japanese

● Full MCP-Mod approach applied only to pooled analysis: same model chosen for pooled analysis also used for Japanese and non-Japanese subgroups
MCP-Mod results – pooled data

- Highly significant DR signal: test statistics for all candidate models with p-values < 0.0001
- Best fitting model selected for MED estimation: Emax
- Estimated MED = 0.9 mg
- Additional estimates:
  - ED50 = 0.36 mg
  - maximum improvement over placebo = 168 mL
Precision of MED and estimated DR model

- Bootstrap approach used to assess precision of estimated MED and fitted DR models

- Subjects were randomly sampled with replacement from their respective dose groups in the original study data, preserving the original sample sizes per dose

- MCP-Mod analysis was repeated for each random sample of subjects, including model selection, MED and DR estimation for each type of analysis

- Confidence intervals (CI) for MED and confidence bands for fitted DR models obtained as percentiles of corresponding MCP-Mod estimates from re-samples (bootstrap CI); average of MED estimates ($MED_B$) also obtained
DR profiles per group, with conf. bands
Bootstrap MED estimates and CI per group

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>( MED_B ) (mg)</th>
<th>90% bootstrap C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled</td>
<td>0.84</td>
<td>[0.48, 1.45]</td>
</tr>
<tr>
<td>Japanese</td>
<td>0.62</td>
<td>[0.24, 1.42]</td>
</tr>
<tr>
<td>non-Japanese</td>
<td>0.90</td>
<td>[0.52, 1.56]</td>
</tr>
</tbody>
</table>
Model-based dose selection

Dose 1mg
- Not much additional gain in efficacy with higher dose
- Concerns about increase in AE incidence
- Equivalent to AC in efficacy, better in safety
Conclusions and further thoughts

- Dose selection for Phase 3 is an estimation problem and should not be addressed via hypothesis testing.

- Model-based dose finding methods are more informative and efficient than pairwise comparisons approaches; should be preferred for dose finding studies.

- Wider dose/exposure ranges (> 10 fold) and larger number of doses/regimens (> 3) should be routinely used in Phase II to allow proper characterization of DR.

- Dose response relationships for both efficacy and safety need to be evaluated to allow adequate estimation of the therapeutic window and benefit/risk.
References

- Koenig et al. (2014) Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod. Presentation at the KOL Lecture Series on “Adaptive Designs”
Dasatinib Dose Optimization: Phase-1 through Phase-3

Amit Roy

FDA-AACR Workshop:
Dose-finding of Small Molecule Oncology Drugs
18-May-2015
Dasatinib is a potent inhibitor of 5 oncogenic tyrosine kinases/kinase families: BCR-ABL, SRC, c-KIT, PDGFB receptor, and ephrin receptor kinases.

**SPRYCEL® (dasatinib) is indicated for the treatment of***:
- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy

The initially approved dose of dasatinib was changed based upon 2 Phase-3 dose optimization studies:
- Initially approved dose: 70 mg BID
- Currently approved doses**
  - CP-CML: 100 mg QD
  - AP, BP, and Ph+ ALL: 140 mg QD

---

*USPI (04/2014)
** CP=chronic phase; AP=accelerated phase; BP=blast phase (myeloid or lymphoid)
Development Timeline

Ph1 Study in CML

5 Ph2 START Studies
- CP-CML (Single Arm)
- CP-CML (vs Imatinib)
- AP-CML
- Myeloid BP-CML
- Lymphoid B-CML, and Ph+ ALL

Ph3 Dose Opt
- CP-CML
- AP-CML

Ph3 1L CML (LT follow-up ongoing)

2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010

Initial NDA (IR/IT)

1L CP-CML sNDA

CP-CML (IR/IT) Dose Opt sNDA

IR/IT: Imatinib resistant/intolerant
Dasatinib inhibited BCR-ABL in a dose dependent manner
Human EC90 was predicted to be ~ 15 ng/mL
Phase-1 Study: CA180002

- Multiple dose escalation study in patients with CP-CML, AP-CML, BP-CML, and Ph+ ALL, with resistance or intolerance to imatinib

- Initial dose escalation
  - 3+3 design
  - 15 to 240 mg QD, 5-days on/2-days off
  - 2-day drug holiday was incorporated to minimize risk of AEs
  - Within subject dose escalation allowed after Cycle-1 (for lack of efficacy)

- Dose regimen amended to continuous (7-day) BID, based upon
  - Preliminary analysis of PK data (T1/2 ~ 3-5 hrs)
  - Observed rebound in blast count over the weekly 2-day drug holiday

- Efficacy endpoints assessed:
  - CHR: Complete hematological response
  - MHR: Major hematological response
  - MCyR: Major cytogenetic response

# Phase-1 Study: Key Efficacy Results (CP-CML)

<table>
<thead>
<tr>
<th>Starting Dose Level</th>
<th>CHR/MHR</th>
<th>MCyR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Responses at Starting Dose*</td>
<td>Number of Responses at Escalated Dose</td>
</tr>
<tr>
<td>Chronic Phase QD Dosing (N=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg QD</td>
<td>1/3</td>
<td>2/2</td>
</tr>
<tr>
<td>30 mg QD</td>
<td>1/3</td>
<td>1/2</td>
</tr>
<tr>
<td>50 mg QD</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td>75 mg QD</td>
<td>1/3</td>
<td>2/2</td>
</tr>
<tr>
<td>105 mg QD</td>
<td>2/3</td>
<td>1/1</td>
</tr>
<tr>
<td>140 mg QD</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td>180 mg QD</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td>Chronic Phase BID Dosing (N=19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg BID</td>
<td>2/3</td>
<td>1/1</td>
</tr>
<tr>
<td>35 mg BID</td>
<td>5/7</td>
<td>0/2</td>
</tr>
<tr>
<td>50 mg BID</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td><strong>70 mg BID</strong></td>
<td><strong>6/6</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

- **MTD was not reached (MAD was 120 mg BID in AP-CML)**
- **70 mg BID was selected as the dose to be investigated in the Phase-2 studies**

Phase-2 Program: START
(SRC/ABL Tyrosine kinase inhibition Activity Research Trials of dasatinib)

- **CA180005**
  A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate

- **CA180006**
  A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Myeloid Blast Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate

- **CA180013**
  A Phase 2 Study to Determine the Activity of BMS-354825 in Subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have Disease that is Resistant to High Dose Imatinib Mesylate (Gleevec®) or who are Intolerant of Imatinib

- **CA180015**
  A Phase 2 Study of BMS-354825 in Subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

- **CA180017**
  A Randomized Multicenter Open Label Study of BMS-354825 vs Imatinib Mesylate (Gleevec®, Glivec®) 800 mg/day in Subjects with Chronic Phase Philadelphia Chromosome-positive Chronic Myeloid Leukemia Who Have Disease That Is Resistant to Imatinib at a Dose of 400 - 600 mg/day

*The dasatinib dose investigated in all Ph2 studies was 70 mg BID*
Phase-2 Studies: Key Results*

Table 4: Summary of Cytogenetic and Hematologic Responses – Percentages of Subjects with Responses – All Treated Subjects in the Single-Arm Phase 2 Studies

<table>
<thead>
<tr>
<th></th>
<th>CA180013 Chronic (N = 186)</th>
<th>CA180005 Accelerated (N = 107)</th>
<th>CA180006 Myeloid Blast (N = 74)</th>
<th>CA180015 Lymphoid Blast (N = 42)</th>
<th>CA180015 Ph' ALL (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic Response Rate (%)</td>
<td>80 (72 - 87)</td>
<td>53 (41 - 64)</td>
<td>36 (22 - 52)</td>
<td>47 (30 - 65)</td>
<td></td>
</tr>
<tr>
<td>OHR (95% CI)</td>
<td>NA</td>
<td>59 (49 - 68)</td>
<td>32 (22 - 44)</td>
<td>42 (26 - 59)</td>
<td></td>
</tr>
<tr>
<td>MaHR (95% CI)</td>
<td>NA</td>
<td>59 (49 - 68)</td>
<td>32 (22 - 44)</td>
<td>42 (26 - 59)</td>
<td></td>
</tr>
<tr>
<td>CHR (95% CI)</td>
<td>90 (85-94)</td>
<td>33 (24-42)</td>
<td>24 (15-36)</td>
<td>26 (3-17)</td>
<td>31 (16-48)</td>
</tr>
<tr>
<td>NEL (95% CI)</td>
<td>26 (18-36)</td>
<td>8 (3-17)</td>
<td>5 (0.6-16)</td>
<td>11 (3.1-26)</td>
<td></td>
</tr>
<tr>
<td>MiHR (95% CI)</td>
<td>21 (14-31)</td>
<td>20 (12-31)</td>
<td>5 (0.6-16)</td>
<td>6 (0.7-19)</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic Response Rate (%)</td>
<td>45 (37-52)</td>
<td>31 (22-41)</td>
<td>30 (20-42)</td>
<td>50 (34-66)</td>
<td>58 (41-75)</td>
</tr>
<tr>
<td>MCyR (95% CI)</td>
<td>33</td>
<td>21</td>
<td>27</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>CCyR (95% CI)</td>
<td>33</td>
<td>21</td>
<td>27</td>
<td>43</td>
<td>58</td>
</tr>
</tbody>
</table>

Efficacy was demonstrated in all the target indications

Table 7: Dose Adjustments Based on 70 mg BID Dosing

<table>
<thead>
<tr>
<th>Disease Phase</th>
<th>Dose Reduction</th>
<th>Dose Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>50%</td>
<td>82%</td>
</tr>
<tr>
<td>AP</td>
<td>45%</td>
<td>73%</td>
</tr>
<tr>
<td>MB</td>
<td>35%</td>
<td>74%</td>
</tr>
<tr>
<td>LB</td>
<td>11%</td>
<td>57%</td>
</tr>
<tr>
<td>Ph+ALL</td>
<td>30%</td>
<td>66%</td>
</tr>
</tbody>
</table>

A high percentage of patients experienced dose reductions or interruptions

*FDA Medical Review (2006)
Nonclinical evidence that continuous inhibition of BCR-ABL may not be necessary for efficacy

Transient inhibition of BCR-ABL by dasatinib leads to apoptosis of CML cells

Phase-3 Dose Optimization Studies

• CA180034:
  ◆ Randomized Two-by-Two, Open-Label Phase III Study
  ◆ Chronic Phase Philadelphia Chromosome or BCR-ABL Positive Chronic Myelogenous Leukemia Who are Resistant or Intolerant to Imatinib Mesylate
  ◆ Dose of 50 mg or 70 mg Twice Daily or 100 mg or 140 mg Once Daily

• CA180035:
  ◆ A Randomized Two-Arm, Open-Label Phase III Study
  ◆ Chronic Myeloid Leukemia in Accelerated Phase or in Myeloid or Lymphoid Blast Phase or with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia who are Resistant or Intolerant to Imatinib Mesylate
  ◆ Dose of 70 mg Twice Daily or 140 mg Once Daily
Key Results: Ph3 Dose Optimization for CP-CML

- Dose optimization was performed in a 4-arm Ph3 study (N ~ 140/arm)
- Primary: Major cytogenetic response (MCyR) at 6-months
  - 70 mg BID: 55%
  - 140 mg QD: 56%
  - 50 mg BID: 54%
  - 100 mg QD: 59%

* Ph+ CML: Philadelphia chromosome-positive chronic myeloid leukemia

Exposure-Response (Efficacy): MCyR at 6-months

- Logistic regression model of Pr(MCyR) at 6-months
- Summary measures of exposure were evaluated as predictors

Effect of Exposure and Covariates on Odds of MCyR at 6-Months

- Weighted Cavgss (wCavgss) was a better predictor of outcome than Cminss or Cmaxss
- Dose maintenance, age, and prior response to imatinib were significant predictors of outcome

Exposure-Response: MCyR (Revisited)

- E-R of MCyR was characterized by an interval-censored parametric (Weibull) TTE model
- Exposure-measure: Time-varying Cavg

Effect of Exposure and Covariates on “Hazard” of MCyR

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavg (140mg:100mg)</td>
<td>(N = 255:279)</td>
</tr>
<tr>
<td>Imatinib Status (resistant:intolerant)</td>
<td>(N = 394:140)</td>
</tr>
<tr>
<td>Race (others:white)</td>
<td>(N = 109:425)</td>
</tr>
<tr>
<td>Sex (female:male)</td>
<td>(N = 280:254)</td>
</tr>
<tr>
<td>Body Weight 75 (32 - 107) kg</td>
<td></td>
</tr>
<tr>
<td>Age 55 (28 - 74.3) yr</td>
<td></td>
</tr>
</tbody>
</table>

Visual Predictive Check of Predicted Time-to-Event of MCyR, by Prior Imatinib Response

- Dose interruptions and modifications were incorporated into the same exposure variable
- Other predictors of MCyR were the same as the previous E-R analysis by logistic regression

Exposure-Response (Safety): Pleural Effusion

• E-R of PE was characterized by a Cox proportional-hazards model of the time to 1st occurrence of a PE (any grade)

• Summary measures of exposure were evaluated as predictors

Effect of Exposure and Covariates on Hazard of Pleural Effusion

- Continuous Reference (5th – 95th Percentile)
- Categorical Comparator: Reference
  - History of Cardiac Disease
    - Yes: No
  - Race
    - Non-caucasian: Caucasian
  - Gender
    - Male: Female
  - Age [yr]
    - 55 (28 – 75)
  - Cminss [ng/mL]
    - 4.33 (2.03 – 8.36)

Hazard Ratio Relative to Reference Value of Covariate

- Cminss was a better predictor of the risk of PE than Cminss or Cmaxss
- Age was a significant predictors of the risk of PE

Summary

• Phase 1 study:
  ◆ Initial dosing regimen was selected based on preclinical and toxicology data
  ◆ Study was amended to include more advanced CML patients, once activity was demonstrated in CP-CML
  ◆ Within subject dose escalation to active doses was allowed
  ◆ Schedule was changed to continuous BID
    – PK data
    – Observed rebound with 2-day drug holiday in initial regimen
  ◆ 70 mg BID was selected as RP2D, based upon efficacy and safety data

• Registrational Phase-2 studies were initiated in multiple stages of CML with RP2D

• Phase-3 dose optimization studies were initiated prior to initial approval based on
  ◆ Emerging data showing transient exposure may be sufficient for efficacy
  ◆ Need to improve safety profile
Some Additional Thoughts (1/2): Challenges in Oncology Dose Selection

• Data on clinical benefit is generally limited prior to Ph3
  • Efficacy endpoints in Ph1/2 oncology studies is often different from the efficacy endpoint in Ph3 oncology studies
  • Uncertainty in extrapolating Ph1/2 efficacy to Ph3
• The dose selection “design space” includes specification of:
  • Dose amount
  • Dosing schedule (often including drug holidays)
• Ph2/3 doses are often selected to be the MTD, typically determined algorithmically (by 3+3 design)
  • DLT period typically does not account for delayed toxicities
  • Does not generally utilize time-course of AE data
• The design space increases combinatorially for drugs being developed as combination therapy
Some Additional Thoughts (2/2): Typical Attributes of Oncology Clinical Data

- Limited data at low doses
  - Most Ph1 studies are some form of a 3+3 design, coupled with a dose expansion cohort (usually at MTD)
  - D-R usually not attempted; E-R generally highly uncertain

- Large variability in overall exposure
  - Dose reductions or interruptions due to AEs are common
  - Wide variability in treatment durations
Acknowledgements

• Xiaoning (Shelly) Wang
• Neelima Thanneer
• Tai-Tsang Chen
Panel Discussion
Session II: Design of Dose-finding Studies

Moderators:
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Statistical Team Leader, DBV
OB, OTS, CDER, FDA

Eric Rubin, MD
Vice President and Therapeutic Area Head,
Oncology Clinical Development, Merck Research Labs

Panelists:
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• Dinesh De Alwis, PhD, Merck Research Labs
• Stuart Bailey, PhD, Novartis Oncology
• José Pinheiro, PhD, Janssen
• Pasi Jänne, MD, PhD, Dana Farber Cancer Institute
• Rajeshwari Sridhara, PhD, Director, DBV, OB, OTS, CDER, FDA
• Donna Dambach, VMD, PhD, Genentech
• Vikram Sinha, PhD, Director, DPM, OCP, OTS, CDER, FDA