Nonclinical Drug Development

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Translational Medicine Early Development
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Disclosure Information
Chris H. Takimoto, MD, PhD

- **Employment**: Ortho Biotech Oncology R&D/Johnson & Johnson PRD
- **Stock**: Johnson & Johnson
- **Off Label Use**: I will not discuss off label use of any products
Lecture Outline

• Nonclinical Drug Development Definitions & Scope

• Components of Nonclinical Drug Development
  – Pharmacology Studies
  – Safety Pharmacology
  – PK/ADME Studies
  – Toxicology
  – Starting Dose Selection for FIH

• Nonclinical Translational Research Strategies
  – Targeted therapies/Biomarkers
  – Pharmacological Audit Trail/Model-based drug development
  – Translational clinical development plans
Nonclinical Drug Development

• **Broad Definition**: All the activities required before a new molecular entity can be administered to humans
  – Spans gap between discovery/screening to FIH clinical trials
  – Provides key pharmacological information about a drug candidate

• **Current Discussion**
  – Focus on pharmacology, safety, toxicology, and translational research strategies in nonclinical development
  – Will not discuss API, CMC, and formulation issues

*Bias Warning!*: Large pharmaceutical, small molecule anticancer drug development perspective
Nonclinical Drug Development
An Industrial Perspective

- Target ID/Validation
  - High-throughput screening
    - 1,000s of compounds
  - Hit to lead
    - 100s of compounds
  - Lead optimization
    - Dozens of compounds
  - Candidate seeking
    - 1–3 compounds
  - Preclinical development
    - GLP toxicology studies: genetic toxicology, safety pharmacology, in vivo toxicity in two species
    - Selectivity assays, in vitro efficacy assays, Tier I ADME/physical chemistry assays
    - Second species PK, PK/PD modelling, salt-form selection, crystal-form assessment
    - In vivo efficacy assays (preclinical POC), Tier II ADME/physical chemistry assays
    - High-throughput screening, IC50 determination, hit triage

- Discovery
- IND Submission
- Clinical Development

Phase I
- Safety and tolerability in normal healthy volunteers
Phase II
- Safety and tolerability in patients, early clinical POP
Phase III
- Definitive clinical POP

Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Guidance for Industry

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2010
ICH
S9 Oncology Specific Guidance

• Applies to targeted small molecules and biopharmaceuticals used for treating “patients with advanced disease and limited therapeutic options”
  – Advanced cancer is a progressive, fatal disease
  – Existing therapies have limited effectiveness
  – Treatment at or close to adverse effect dose levels

• The type, timing, and flexibility of oncology studies may differ from other therapeutic areas

• Does NOT apply to cancer prevention, supportive care, healthy volunteers, radiopharmaceuticals, vaccines, cellular or gene therapies

-- S9 Guidance for Industry, 2010
S9 Oncology Specific Guidance
Goals of Nonclinical Testing

1. Identify the pharmacologic properties of a pharmaceutical

2. Understand the toxicological profile of a pharmaceutical

3. Establish a safe initial dose level of the first human exposure

-- S9 Guidance for Industry, 2010
Nonclinical Pharmacology Models

• Recommendations for Model Selection

  – Select nonclinical models appropriate to target and anticipated activity

  – But “need not be studied using the same tumor types intended for clinical evaluation”

-- S9 Guidance for Industry, 2010
Nonclinical Drug Development
In Vitro Pharmacology Models

• In vitro studies performed in cell lines or cell-free systems
  – Often form the basis for screening and optimization during discovery

• Oncology uses human tumor cell lines for evaluation of:
  – Mechanism of action
  – Evaluation of potency and selectivity
  – Early indication selection
  – Predictive biomarker discovery

-- S9 Guidance for Industry, 2010
In Vitro Cell Line Analyses

Cisplatin

Carboplatin

Cell Lines

Relative Potency (GI_{50})
Limitations of 2D Tumor Models

Tumor Microenvironment

Humanized 3D Models
(for Advanced Biomarker and Drug Discovery Applications)

Standard 2D Culture  3D-TGA  'Humanized' 3D-TGA

Tumor cells alone or co-culture  Tumor cells alone in 3D IrBME  Tumor cells + (10:1) hMSC/hCAF in 3D IrBME

'TME-Aligned' 3D-TGA  'Humanized' xenografts

Tumor cells + (10:1) hMSC/hCAF + hormones, pH, glucose in 3D IrBME

Tumor cells + (10:1) hMSC/hCAF + hormones in 3D IrBME implanted into xenografts

Abbreviations: TGA, tumor growth assay; IrBME, Irradiated basement membrane extract; hMSC, human mesenchymal stem cells; hCAF, human cancer associated fibroblasts; TME, tumor microenvironment

-- B. Hall, Ortho Biotech Oncol R&D
3D-TGA: Diverse Biologic Applications

- Flow Cytometry
- DNA/RNA Extraction
- Proliferation & Growth
- Pharmacology Studies
- Protein Assays
- Histopathology
- 3D Imaging & Morphology
- Humanized *in vivo*
- Human TME-alignment
- Biomarker Discovery


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*B. Hall, Ortho Biotech Oncol R&D*
In Vivo Animal Models

• The ideal animal model should be:
  – Valid
  – Selective
  – Predictable
  – Reproducible

“There is no perfect tumor model”
“All models are wrong, some are useful”
Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth
Nonclinical Drug Development
Utility of In Vivo Pharmacology Models

• Rodent tumor models form the cornerstone for oncology nonclinical testing
  – But in vivo models are too expensive for routine HTS use

• Demonstration of proof of principle
  – Antitumor efficacy in living host

• Evaluation of therapeutic index
  – Toxicity versus efficacy

• Early assessment of PK-PD relationships
  – Drug exposure and endpoint correlations
  – Dose and schedule selection
  – ADME data can be generated in parallel with clinical development

• Preliminary evaluation of candidate biomarkers
In Vivo Efficacy Models in Cancer

• Spontaneous tumors
  – Idiopathic
  – Carcinogen-induced
  – Transgenic/gene knockout animals: p53, RB, etc

• Transplanted tumors
  – Syngeneic animal tumors: Lewis lung, S180 sarcoma, B16 melanoma murine tumors
  – Human tumors growing in vivo in implantable hollow fibers
Human Tumor Xenografts Models

- Most common in vivo preclinical efficacy models in oncology
  - Current NCI standard in vivo efficacy testing system
- Consist of human tumor cells implanted in immunocompromised animals
  - Nude mice
  - SCID mice
  - Nude rats
- Diverse human tumor cell lines propagated in vitro can grow as xenograft models
Nude Mouse Hosts for Xenograft Studies

- Athymic “nude” mice developed in 1960’s
- Mutation in nu gene on chromosome 11
- Phenotype: retarded growth, low fertility, no fur, immunocompromised
  - Lack thymus gland, T-cell immunity
- First human tumor xenograft of colon adenocarcinoma by Rygaard & Poulson, 1969
Differential Tumor Growth of Prostate Cancer Xenografts

(Mahajan, Cancer Res 2005;65:10514)
Xenograft Advantages

• Diverse selection of different human tumor types
  – Molecular characterization, GEP, available in public databases

• Ease and speed of start up and conduct of studies

• Simultaneous evaluation of safety and efficacy (therapeutic index)

• Some correlation with clinical activity lung, colon, breast, and melanoma cancers

• Although subcutaneous implantation is most common, orthotopic injections are possible
  – Mammary fat pad, CNS, intraperitoneal, etc

• Wide accessibility

• Many decades of experience
Xenograft Disadvantages

- Atypical biological behavior
  - Metastases are rare
  - Survival not an ideal endpoint, with historical deaths from tumor bulk, not invasion
  - Short doubling times
  - Less necrosis, better blood supply

- Positive predictive value is poor

- Poorly mimics the tumor microenvironment
  - Human tumor cells with murine stroma
  - Host directed therapies (immunomodulation, stromal tissue targets) may not be applicable
    - Species specific differences between humans and mice
  - Examples: Antibody biopharmaceutics that only recognize human targets
Low Passage Patient Tumorgrafts

Primary human tumors


(Courtesy of W. Hait)
**Patient Tumorgraft Clinical Correlations**

**Colorectal Tumorgraft**
(Estrada et al, EORTC-NCI-AACR, 2010)

<table>
<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>Irinotecan (100) (p&lt;0.005)</th>
<th>Cetuximab (20) (p&lt;0.005)</th>
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<td>35</td>
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**CLINICAL OUTCOME**

**RESPONDED TO:** FOLFOX, FOLFIRI/BEVA

**FAILED:** NONE

(Courtesy of M. Wick, START Laboratories)
Transgenic Animal Models of Cancer

- P53 or other tumor suppressor gene knockout animals have high incidence of endogenous tumor development
- Theoretically more directly analogous to human situation
- Advantages
  - Intact immune system
  - Murine tumor and stroma
  - Better for cancer prevention
  - May be engineered for specific purposes
- Disadvantages
  - Long experimental start up times
  - Variable penetrance
  - Monitoring tumor growth in individual animals is challenging
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Safety Pharmacology Studies

- Core battery of **required** safety pharmacology tests (ICH S7A, Section 2.7)
  - Central Nervous System
  - Cardiovascular System
  - Respiratory System

- Additional supplemental studies must be individualized for each drug
  - May incorporate into general toxicology studies

- Oncology recommendations (S9 Guidance)
  - Vial organ assessment still required, but may not need stand alone safety studies in the absence of specific risk
  - Incorporate core vital organ evaluations into cGLP toxicology studies

- References
  - S9 Guidance 2010
  - S7A Safety Pharmacology Studies for Human Pharmaceuticals, 2000
Safety Pharmacology Studies
QTc Prolongation Risk Assessment

• Prolonged QTc caused by delayed ventricular repolarization
  – Increased risk of ventricular arrhythmias, especial Torsade de Pointes
  – Increased risk with hypokalemia, structural heart disease, or bradycardia

• Late repolarization of cardiac action potential
  – Mediated by efflux of K+ ($I_{Kr}$ and $I_{Ks}$) through delayed rectifier K+ channels

• Human ether-a-go-go-related gene (hERG)
  – Encodes the alpha subunit of the human K+ channel proteins responsible for $I_{Kr}$
  – Basis for preclinical in vitro testing for QTc prolongation risk

• Pharmaceuticals that prolong QTc can have proarrhythmic effects

• References
  – S7B, Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization, 2005
Nonclinical QTc Testing Strategy (ICH S7B, 2005)

- Routine Nonclinical Tests
  - In Vitro \( I_{Kr} \) (hERG) assay, and
  - In vivo QT assay in nonrodent species
    - May incorporate CV core battery study
    - Assess chemical/pharmacological class for choice of reference compounds

- Integrated Risk Assessment
  - Consider all relevant nonclinical information
  - Consider follow up studies
    - Action potential, Rabbit wedge, etc

- Determine Evidence of Risk
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Nonclinical PK/ADME Studies for Oncology Studies

• Limited pharmacokinetic parameter estimation in nonclinical animal species
  – Cmax, AUC, and half-life

• Use to facilitate dose selection, schedule, and escalation in Phase 1

• Additional nonclinical ADME studies should be generated in parallel with clinical development (!!)

• Reference
  – S9 FDA Guidance 2010
Nonclinical PK/ADME Studies

- Cellular uptake and membrane transport
  - MDR (P-glycoprotein), MRP, etc.
  - Predictions of bioavailability and distribution

- In vitro drug metabolism
  - P450 isoenzyme metabolism, inhibition or induction

- Plasma protein binding studies
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Nonclinical Toxicology Studies in Oncology

- IND-Enabling general toxicology studies
  - Use the same route and formulation as clinical trial
  - Approximate the clinical schedule

- Small molecule toxicology testing usually includes rodents and non-rodents (i.e., dogs)
  - Non-human primates for biologicals

- Assess the potential to recover from toxicity
  - Terminal non-dosing period recommended
  - Complete recovery demonstration is not essential

- Toxicokinetics evaluations as appropriate

-- S9 Guidance for Industry, 2010
Good Laboratory Practice (GLP)

- Most safety pharmacology and toxicology studies should be conducted with GLP
  - Full GLP may not be feasible in some safety pharmacology studies

- All core battery safety pharmacology studies should be GLP

- Primary pharmacodynamic (general pharmacology) studies do not need to be conducted in compliance with GLP (S7A Section 2.11)
Reproduction Toxicology

- Embryonic and fetal toxicology studies required at the time of marketing application
  - Exceptions for genotoxic agents that target rapidly dividing cells or known developmental toxins

- Typically conducted in two different species
  - Biologicals may use one relevant species

- Fertility and early embryonic development studies are not required for use in advanced cancer patients

- Pre- and post-natal toxicology studies not warranted for oncology
Other Toxicology Studies (S9)

• Genotoxicity
  – Not essential for oncology clinical trials
  – Should be performed to support marketing application

• Carcinogenicity
  – Not warranted for marketing in oncology patients

• Immunotoxicity
  – May evaluate in general toxicology studies for oncology
  – May require more extensive study for known immunomodulators

• Photosafety testing
  – Initial phototoxic potential assessment prior to Phase 1 based upon known photochemical properties
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and study design issues for FIH
Staring Dose for First in Human Studies in Oncology

• **Goal:**
  – Select a start dose that is expected to have pharmacological effects and is reasonably safe to use

• Based on all available nonclinical data

• Scale up from animal studies
  – For small molecules, normalize to body surface area
  – For biologicals, scale to body weight, AUC or other exposure parameters
Study Design Issues for FIH Oncology Trials

- Doses or exposures tested in nonclinical studies do NOT limit the highest dose in an oncology patient trial

- Planned dose escalation increments should scale to the steepness of the nonclinical dose-response (toxicity) curves
Duration of Nonclinical Toxicology Studies

• Treatment duration in Phase 1 oncology may continue according to patients response
  – New toxicology studies not required

• Phase 2 studies may be supported by existing nonclinical and clinical Phase 1 data
  – Additional toxicology not required

• Phase 3 studies may require repeat dose studies of 3 months duration
  – Sufficient to support marketing

• New drug combination regimens do not require specialized toxicology studies
  – In vivo pharmacology studies of the combination may suffice
## Treatment Schedules to Support Initial Oncology Trials

*(S9 Guidance for Industry, March 2010)*

<table>
<thead>
<tr>
<th>Clinical Schedule</th>
<th>Nonclinical Treatment Schedule *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once every 3-4 wks</td>
<td>Single dose</td>
</tr>
<tr>
<td>Daily for 5 days every 3 wks</td>
<td>Daily for 5 day</td>
</tr>
<tr>
<td>Daily for 5-7 days, alternating wks</td>
<td>Daily for 5-7 days, alternating wks (2-dose cycles)</td>
</tr>
<tr>
<td>Once a week for 3 wks, 1 wk off</td>
<td>Once a week for 3 weeks</td>
</tr>
<tr>
<td>Two or three times a week</td>
<td>Two or three times a week for 4 wks</td>
</tr>
<tr>
<td>Daily</td>
<td>Daily for 4 wks</td>
</tr>
<tr>
<td>Weekly</td>
<td>Once a week for 4-5 doses</td>
</tr>
</tbody>
</table>
Oncology Small Molecule Dose Selection

• In oncology, the start dose at 1/10 the severely toxic dose in 10% of animals (STD10) in rodents

• If non-rodent is most appropriate species, then 1/6 the highest non-severely toxic dose (HNSTD)
  – HNSTD is the highest dose level that does not produce evidence of life-threatening toxicities or irreversible findings

-- S9 Guidance for Industry, 2010
Biologicals: MABEL Instead of NOAEL, MAYBE?

- New European recommendations based upon Tegenero FIH disaster,
  - EMEA Guidelines, 2007

- MABEL: minimal anticipated biological effect level
  - Consider differences in sensitivity for the mode of action across species

- Consider selection of starting doses based upon reduction from the MABEL
Calculation of MABEL
(EMEA Guidelines, 2007)

• MABEL calculations should utilize nonclinical data available, including…
  – Target binding and receptor occupancy data in target cells in vitro in human and animals
  – Concentration-response curves in vitro
  – Dose/exposure-response in vivo in relevant animals

• Wherever possible an integrated PK/PD modeling approach should be used

• Apply a safety factor to the MABEL for the recommended starting dose (i.e., 1/10 MABEL)
Nonclinical Translational Research Strategies in Drug Development
The Drug Discovery & Development Pipeline

Discovery

- Target-to-hit: 24
- Hit-to-lead: 19
- Lead optimization: 15
- Preclinical: 12

Development

- Phase I: 9
- Phase II: 5
- Phase III: 2
- Submission to launch: 1

New Projects Per Year:
- 24
- 19
- 15
- 12

Success:
- 80%
- 75%
- 85%
- 69%
- 54%
- 34%
- 70%
- 91%

Time (yr):
- 1.0
- 1.5
- 2.0
- 1.0
- 1.5
- 2.5
- 2.5
- 1.5

Cost (USD):
- $94
- $166
- $414
- $150
- $273
- $319
- $34
- $48

Total time = 13.5 years
Total cost = $1.778 billion*

* Capitalized costs

-- Modified from Paul et al, Nature Rev Drug Discov 2010
A Blueprint for a Restructured Drug Development Organization

- How to make better decisions at POC?
- How to improve the probability of success (pTS) in Phase 2b and 3?

\[ P \approx \frac{WIP \times pTS \times V}{C \times CT} \]

-- Modified from Paul et al, Nature Rev Drug Discov 2010
Our Translational Strategy

- Focus on **Molecularly Targeted Therapies** with strong **Biomarker** support
- **Pharmacological Audit Trail (PhAT)** evaluation in preclinical and early clinical trials
- **Model-based Drug Development** approach initiated during preclinical stages
- Novel biomarker-driven **Phase I FIH study designs** translational clinical development plans
### Characteristics of Molecularly Targeted Therapies

*(adapted from Paoletti 2005)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cytotoxic Agents</th>
<th>Targeted Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discovery</strong></td>
<td>Cell based, empirical</td>
<td>Receptor based screen, rationale</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Often unknown</td>
<td>Basis for screening</td>
</tr>
<tr>
<td><strong>Pharmacological Effect</strong></td>
<td>Cytotoxic</td>
<td>Cytostatic</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Non-selective</td>
<td>Selective</td>
</tr>
<tr>
<td><strong>Dose and schedule</strong></td>
<td>Pulsed, cyclical at MTD</td>
<td>Continuous, at tolerable dose</td>
</tr>
<tr>
<td><strong>Development Strategy</strong></td>
<td>Biomarkers for decision making is rare</td>
<td>Biomarkers for PD/MofA and patient selection</td>
</tr>
</tbody>
</table>
The Biomarker Hypothesis
(adapted from Nic Dracopoli)

The use of biomarkers will....

• Improve decision making in early development
  – Early proof of mechanism of action
  – Selection of optimal dose and schedules
  – Better understanding of pharmacological behavior through PhAT evaluation
  – Better Go/No Go Proof of Concept decisions

• Increase probability of technical and registrational success (PTRS) in late stage development
  – Smaller, more focused, enriched study populations
  – Greater magnitude of clinical benefit

• Provide greater benefits for our patients through personalized medicine
  – Enable more cost-effective delivery of healthcare
  – Value-based pricing
  – Faster uptake and higher market penetration

The use of biomarkers will....
Types of Biomarkers in Most Relevant to Drug Development

- **Pharmacodynamic/Mechanism of Action Biomarkers**
  - Biomarkers that inform about a drug’s pharmacodynamic actions
  - What is the drug doing in the patient and/or tumor?

- **Predictive Biomarkers**
  - Optimize patient selection by selecting subpopulations for treatment
  - Who should or should not get this drug?
  - Basis for stratified/personalized medicine strategies
Translational Research Timelines

Drug Development Timeline

- **PD/MofA Biomarkers**
  - Marker ID/Qualification
  - PK/PD Biomarker studies
  - Clinical robustness in tumor and surrogate tissues
  - Applied to clinical trials
  - Aid in PhAT evaluation

- **Predictive Biomarkers**
  - Marker ID/Qualification
  - In vitro/In vivo confirmation
  - Clinical applicability
  - Exploratory clinical testing
  - Clinical qualification as a co-diagnostic
  - Deliver a companion diagnostic at launch
The Pharmacological Audit Trail

Commentary

Auditing the Pharmacological Accounts for Hsp90 Molecular Chaperone Inhibitors: Unfolding the Relationship between Pharmacokinetics and Pharmacodynamics

Paul Workman
Cancer Research UK, Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey SM2 5NG, United Kingdom

1. Conceptual facts, such as the inhibition of proliferation, cell cycle progression, survival, invasion, or angiogenesis, and the achievement of a clinical response. By making measurements at each of these hierarchical levels of drug action, it is possible...

The Pharmacological Audit Trail
(from Workman et al, Mol Cancer Therap 2003)

Is the target expressed or activated?
Adequate drug dose & schedule?
Active concentrations in plasma?
Active concentrations in tumor?
Active against the molecular target?

Modulation of downstream pathway?
Biological effect achieved?
Clinical response or benefit?
Predictive biomarkers of activity?
Proof of Concept achieved?

Reduce Uncertainty
Reduce Uncertainty

Unknown
Weak
Established
Strong
Model Based Drug Development Example

cMET Inhibition

Sacrifice a subset at 1, 4, 8, and 24 h (n = 3 per time point)

- Plasma
- Tumor

Dose at 3.1, 6.3, 12.5, 25, and 50 mg/kg

Tumor Growth Inhibition

Plasma PK Analysis

Assay Tumor PD Biomarker

-- Yamazaki et al Drug Met Dispos 2008
Model Based Drug Development

**Pharmacokinetics**

- **PK in Plasma**
  \[ C_p = \left( \frac{F \cdot \text{Dose} \cdot k_a}{V \cdot (k_a - k)} \right) \left( e^{-k \cdot t} - e^{-k_a \cdot t} \right) \]

- **PK Simulation in Tumor**
  \[ \frac{dC_e}{dt} = k_c \cdot (C_p - C_e) \]

**Pharmacodynamics**

- **cMet Phosphorylation**
  \[ E = E_0 \left( 1 - \frac{E_{max} \cdot C_e}{EC_{50} + C_e} \right) \]

- **Tumor Growth Inhibition**
  \[ \frac{dT}{dt} = k_a \left( 1 - \frac{E_{max} \cdot C_p}{EC_{50} + C_p} \right) \cdot T \cdot k_{out} \cdot T \]

- **Plasma PK** ➔ **Tumor PK** ➔ **Biomarker Change** ➔ **Antitumor Activity**

(Yamazaki et al Drug Met Dispos 2008)
Translational Phase I Study with Biomarker-Defined Endpoints

- **Expansion Cohorts**
  - Collect mandatory sequential tumor biopsies
  - Examine molecularly defined subsets of various tumor types
  - Early readout on predictive biomarker hypothesis

- **Dose Escalation** with PD biomarker monitoring in surrogate tissue
- **Target PD biomarker effect in surrogate tissues or if any clinical activity**
- **Potential Phase 2 Dose Range**
- **Maximum Tolerated Dose**
- **“BAD”**
- **“MTD”**
- **“DLT”**

- Expansion Cohort 3
- Expansion Cohort 2
- Expansion Cohort 1

Tumor biopsies and/or Predictive biomarker selected pts
Clinical Development in 2011 and Beyond

**Translational Phase 1 Trials**
- Phase 1 Multiple Tumors
  - Assess PK, MTD, biological activity & pt selection
  - Phase 1 Expansion Cohort A
  - Phase 1 Expansion Cohort B
  - Phase 1 Expansion Cohort C
  - Phase 1 Expansion Cohort D

**PBM Selected Phase 2 Trials**
- Phase 2 POC Disease
  - Phase 2 Tumor Type C
  - Phase 2 Tumor Type D

**Small Enriched Phase 3 Trials**
- Phase 3 in POC Disease
  - Phase 3 Tumor Type B
  - Phase 3 Tumor Type C

No efficacy

Predictive Biomarker Identification → Qualification
Summary

• Nonclinical drug development involves the collection of key pharmacology, safety, toxicology, and PK/ADME data prior to the initiation of FIH studies

• Strict regulatory requirements regarding data needed for IND submission

• Key period for formulating Translational Research plans for clinical development
And Finally….

Translational Medicine

Nonclinical Pharmacology
- Efficacy/Safety
- Traditional animal studies
- PK/PD Toxicology
- Biomarkers & Molecular targets

Clinical Pharmacologist

“Model-based drug development”

Early Clinical Trials
- Traditional dose and toxicity endpoints
- Traditional PK/PD Biomarkers & Molecular endpoints
- Patient selection

It is a great time to be in drug development!