Nonclinical Drug Development

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Experimental Medicine Early Development
Oncology Therapeutic Area
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March 2015
Disclosure Information
Chris H. Takimoto, MD, PhD

- **Employment**: Janssen R&D/Johnson & Johnson
- **Stock**: Johnson & Johnson
- **Off Label Use**: I will not discuss off label use of any products
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, 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

Phase I

Phase II

Phase III

Clinical development

Target ID/Validation
High-throughput screening, IC₅₀ determination, hit triage

Selectivity assays, in vitro efficacy assays, Tier I ADME/physical chemistry assays

In vivo efficacy assays (preclinical POC), Tier II ADME/physical chemistry assays

Second species PK, PK/PD modelling, salt-form selection, crystal-form assessment

GLP toxicology studies: genetic toxicology, safety pharmacology, in vivo toxicity in two species

Safety and tolerability in normal healthy volunteers
Safety, dose recommendation, and early POC in cancer patients

Safety and tolerability in patients, early clinical POP

Definitive clinical POP

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

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

3. Understand the **toxicological profile** of a pharmaceutical

-- 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
In Vitro Cell Line Analyses

Cisplatin

Carboplatin

Cell Lines

Relative Potency ($G_{I50}$)
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’
‘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

Complexity & TME-relevance

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, Janssen 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

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
    - Valuable for immune-based therapies
  - 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 biopharmaceuticals that only recognize human targets
Patient-Derived Xenograft Models

Consented patient → Surgically removed tumour ($F_0$) → Engraftment phase ($F_1$) → Expansion phase ($F_2$) → Treatment phase ($F_3$ → $F_n$)

- Biologic studies
- Biomarker discovery
- Perpetual bank

Predictive biomarker development and validation

- Mutational status
- Copy number variation
- Gene expression

Integrative genomic classifier

Clinical trials

Biomarker positive

Drug X

Biomarker negative
Low Passage Patient Tumorgrafts

Primary human tumors


(Courtesy of W. Hait)
Patient Tumorgraft Clinical Correlations

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

Myoepithelial Salivary Gland Tumorgraft

Subcutaneous Implant

Salivary Metastases

(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
Transgenic Animal Models

(b) Germline mutation in oncogene and/or TSG (e.g., ApcMin+), 20+ weeks → Tumor-bearing GEMM → Drug treatment + → Quantify tumor number and size at necropsy

(c) Conditional GEMM (e.g., ApcLoxP16114/LoxP16114), Somatic activation of oncogene and/or inactivation of TSG with Adeno-Cre, 4+ weeks → Tumor-bearing GEMM → Drug treatment + → Pre-treatment colonoscopy, size measurement → Post-treatment colonoscopy, size measurement

Cre-Lox System

Trends in Pharmacological Sciences
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

• For non-oncology agents, a core battery of safety pharmacology tests is **required** (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)
  – Vital 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 IKr
  - 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
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- 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**

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*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 Guidance Section 2.11
Reproduction Toxicology
(S9 Guidance)

• Embryonic and fetal toxicology studies required at the time of marketing application
  – In rare cases may not need at all 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

-- S9 Guidance for Industry, 2010
Other Toxicology Studies
(S9 Guidance)

- **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

-- *S9 Guidance for Industry, 2010*
Components of Nonclinical Drug Development

- Pharmacology Studies/Model Selection
- Safety Pharmacology
- PK/ADME Studies
- Toxicology
- Starting Dose Selection and Study Design Issues for FIH
Starting 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

-- *S9 Guidance for Industry, 2010*
Duration of Nonclinical Toxicology Studies

- Treatment duration in Phase 1 oncology may continue according to patients response
  - New nonclinical 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

-- S9 Guidance for Industry, 2010
# Treatment Schedules to Support Initial Oncology Trials

 (*S9 Guidance for Industry, March 2010*)

<table>
<thead>
<tr>
<th><strong>Clinical Schedule</strong></th>
<th><strong>Nonclinical Treatment Schedule</strong></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 ($STD_{10}$) 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 (super agonist CD-28 mAb) 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**
- New Projects Per Year: 24
- Target-to-hit: 80%
- Hit-to-lead: 75%
- Lead optimization: 85%
- Preclinical: 69%
- Time (yr): 1.0
- Cost (USD): $94

**Development**
- Phase I: 9
- Phase II: 5
- Phase III: 2
- Submission to launch: 1
- Success: 54%
- Time (yr): 1.5
- Cost (USD): $273

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

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

* Capitalized costs
A Blueprint for a Successful Drug Development Organization

**a Traditional**
- Scarcity of drug discovery
  - CS
  - Preclinical development
  - Phase I: FHD
  - Phase II: FED
  - Phase III: PD
  - Launch

**b Quick-win, fast-fail**
- Abundance of drug discovery
  - CS
  - Preclinical development
  - POC
  - Confirmation, dose finding
  - Higher PD
  - Launch

- Increase critical information content early to shift attrition to an earlier, cheaper phase
- Leverage savings from shifted attrition to reinvest in the R&D ‘sweet spot’

Paul et al, Nat Rev Drug Discov 2010
Our Translational Strategy

• Focus on **Molecularly Targeted Therapies**

• Integration of **Biomarker Strategies** into clinical development plans

• Utilize a **Model-based Drug Development** approach initiated during preclinical stages

• Implement novel biomarker-driven translational **Phase I FIH study designs**

• **Pharmacological Audit Trail (PhAT)** evaluation in preclinical and early clinical trials
### 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>Discovery</td>
<td>Cell based, empirical</td>
<td>Receptor based screen, rationale</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Often unknown</td>
<td>Basis for screening</td>
</tr>
<tr>
<td>Pharmacological Effect</td>
<td>Cytotoxic</td>
<td>Cytostatic</td>
</tr>
<tr>
<td>Specificity</td>
<td>Non-selective</td>
<td>Selective</td>
</tr>
<tr>
<td>Dose and schedule</td>
<td>Pulsed, cyclical at MTD</td>
<td>Continuous, at tolerable dose</td>
</tr>
<tr>
<td>Development Strategy</td>
<td>Biomarkers rarely used</td>
<td>Biomarkers for PD/MofA and CoDx for 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

(adapted from Nic Dracopoli)
Predictive Biomarker/CoDx Timelines

- **Drug Development Timeline**
  - Target ID/Valid.
  - NME
  - Ph I/II
  - Ph III
  - NDA

- **PD/MofA Biomarkers**
  - Marker ID/Qualification
  - PK/PD Biomarker studies
  - Clinical robustness in tumor and surrogate tissues
  - 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

- **Companion Diagnostics**
  - Assay and software validation
  - Reagent and instrument manufacture under Quality Systems Regulations
  - FDA submission
  - Co-promotion with Rx
Model Based Drug Development Example

cMET Inhibition

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

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

Plasma PK Analysis

Tumor Growth Inhibition

Assay Tumor PD Biomarker

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

**Pharmacokinetics**

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

- **PK Simulation in Tumor**
  \[ \frac{dC_e}{dt} = k_c 0 \cdot (C_p - C_e) \]

- **Pharmacodynamics**

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

  - **Tumor Growth Inhibition**
    \[ \frac{dT}{dt} = k_{a1} \left(1 - \frac{E_{max} \cdot C_p}{EC_{50} + C_p}\right) \cdot T - k_{out} \cdot T \]

- **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

- **“BED”**
  - Target PD biomarker effect in surrogate tissues or if any clinical activity

- **“MTD”**
  - Potential Phase 2 Dose Range
  - Maximum Tolerated Dose

- **“DLT”**
  - Tumor biopsies and/or Predictive biomarker selected pts
Improving Scientific Rigor for Dose Selection
The Pharmacological Audit Trail (PhAT V. 2.02)

- Dose-PK/exposure predictable?
- Active plasma concentrations achieved?
- Target engaged?*
- Modulation of downstream pathway?*
- Biological effect achieved?*
- Target modulating dose sustainable, and tolerable?
- Clinical response or benefit?
- Predictive biomarkers of activity?
- POC population defined?
- POC Decision!

Reduce Uncertainty

* Requires PD Biomarkers for Dose Selection

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Modified from Workman et al, Mol Cancer Therap 2003
How is Drug Development Changing?

**Historical Approach: A linear, sequential process**

- IND Studies
- Phase 1
- Phase 2
- Phase 3
- Launch

**Accelerated, Flexible ED Plans: Early efficacy signals trigger acceleration**

- IND Studies
- Phase 1/2a/POC
- Phase 3
- Launch
**Accelerated ED Study Designs:**

**Dabrafenib/Trametinib Ph 1/2a/2b**

**A. Dose Escalation**

- **MTD or Full MonoRx Dose**
- **PK, tolerability**
- **3+3 Dose Escalation**
  - **D150 + T2**
  - **D150 + T1.5**
  - **D150 + T1**
  - **D75 + T1**

**B. Expansion Cohorts**

- **BRAF mut**
  - **Melanoma**
  - **Colorectal**

**C. Randomized POC Cohorts**

- **Dabrafenib**
  - **N = 54**
- **Dab/Trametinib 1 mg**
  - **N = 54**
- **Dab/Trametinib 2 mg**
  - **N = 54**

Endpoints:
- **PFS, RR, incidence of SqCC**

**N = 247 patients(!) in parts 1b and 2b enrolled from March 26, 2010 to July 7, 2011 at 16 centers**

Flaherty et al 2012
Summary

• Nonclinical drug development involves the collection of key pharmacology, safety, toxicology, and PK/ADME data prior to the initiation of FIH studies
  – Oncology program have slightly different requirements

• Key period for formulating Translational Research plans for clinical development

• Translational drug development clinical trials are evolving but are based upon scientific principles derived from nonclinical studies
And Finally…. 

Translational Medicine

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

Clinical Pharmacologist

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

"Model-based drug development"

It is a great time to be in drug development!