Determining Dose in the Era of Targeted Anticancer Therapies

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Clinical Trial Process

• 1906: **Pure Food and Drugs Act** - protect against misbranding and adulteration of foods, drinks, and drugs

• 1938: **Food, Drug and Cosmetic Act** – pre-market proof of safety (in response to elixir sulfanilamide, which contained a solvent analog of antifreeze, resulting in deaths)

• 1962: **Kefauver–Harris Amendment** to the 1938 Food, Drug, and Cosmetic Act (in response to birth defects arising from thalidomide) required that sponsors seeking approval of new drugs demonstrate the drug's efficacy, in addition to its safety, through a formal process that includes "adequate and well-controlled" clinical trials as the basis to support claims of effectiveness.

• 1970: first **package insert** required (information for patients on risk/benefits)

• 1997: **Regulatory Modernization Act**: Creates a law allowing FDA to “fast track” products

• 2012: **FDA Safety and Innovation Act (FDASIA)** - 'breakthrough therapy designation’
Drug Development Pipeline

12-16 years

Target Identification and Validation  Hit Finding  Lead Optimization  Early Clinical Safety and Efficacy  PoC/Phase I trials  Phase II trials  Phase III trials  Registration  Post-launch activities

Drug Discovery  Early Development  Full Development

Targets  Therapeutics

The Average Cost to Develop One New Approved Drug — Including the Cost of Failures

Thousands to Millions of Compounds Screened

Multiple Leads per Target

R&D Valley of Death

$1.4B  $3B  $4B (mid-1990s)  $12B (early 2000s)
Stages of Clinical Research

**Phase I**
- First-in-human trials: Safety and tolerability; Dose across tumor types
- How much to give and how?
- 20-30 patients

**Phase II**
- Determine clinical benefit in patients with a type of disease
- Does it work in some patients with one type of disease?
- 50-100 patients

**Phase III**
- Compare to existing standard of care
- Does it work better than what is already out there?
- >500-3000 pts

**Phase IV**
- Post-marketing safety studies
- Is it safe in large populations?
- 1000s of patients
The Purpose of Toxicology Evaluation in Drug Development

Toxicology studies are not about proving the safety of a molecule.

They are intended to characterize the sequence and extent of adverse effects as they relate to dose/exposure.

Performed in two mammalian species, usually rat and dog. Have to be conducted in accordance with Good Laboratory Practices (21CFR 58)

Recommended reading-The no-observed-adverse-effect-level in drug safety evaluations: Use, issues, and definition(s), Michael A. Doratoa and Jeffery A. Engelhardt
Regulatory Toxicology and Pharmacology Volume 42, Issue 3, August 2005, Pages 265-274
The Concept of “Margin of Safety”

The NOAEL is the dose on the toxicology dose–response curve that is compared to the pharmacodynamic effective dose to establish the MOS.

Highest Dose/Exposure Associated with No Toxicity (NOEL) or “Manageable” Toxicity (NOAEL)

Efficacious Dose/Exposure in Appropriate Test System
Maximum Recommended Starting Dose (MRSD) for First In Human Trials

- **Step 1:** Determination of the No Observed Adverse Effect Level (NOAEL)
- **Step 2:** Conversion of NOAEL to Human Equivalent Dose (HED)
- **Step 3:** Selection of the most appropriate animal species
- **Step 4:** Application of a safety factor to determine MRSD
- **Step 5:** Compare MRSD with pharmacologically active dose (PAD)
- **Selection of MRSD**
Toxicity driven dosing: Hypothetical dose-response and dose-toxicity (DLT) curves

![Graph showing dose-response and dose-toxicity curves. The x-axis represents Dose Level, ranging from 1 to 7, and the y-axis represents Probability of Outcome, ranging from 0.0 to 1.0. Two curves are shown: one for Response (red) and one for DLT (blue). The graph highlights a dose level of 4 where the DLT curve intersects with the y-axis at 0.4, indicating a certain probability of toxicity at this dose level.]
Dose Escalation

• Rule-based designs:
  • Assign patients to dose levels according to pre-specified rules based on actual observations of target events (e.g., the dose-limiting toxicity) from the clinical data. (3+3 design)

• Model-based designs:
  • Assign patients to dose levels and define the MTD for phase II trials based on the estimation of the target toxicity level by a model depicting the dose–toxicity relationship. (Continuous reassessment method)
Phase I Trial Designs

• **Traditional 3+3 design:**
  - Treat 3 patients at dose D:
  - If 0 patients experience a DLT, escalate to dose D+1
  - If 2 or more patients experience DLT, de-escalate to level D-1
  - If 1 patient experiences DLT, treat 3 more patients at dose level D
    - If 1 of 6 experiences DLT, escalate to dose level D+1
    - If 2 or more of 6 experiences DLT, de-escalate to level D-1
  - The MTD is defined as the highest dose at which 0 or 1 patient out of 6 enrolled at the dose have a DLT.

• Modified Fibonacci sequence: the dose first increases by 100%, and then 67%, 50%, 40%, and 30%–35% of the preceding doses

• An excessive number of escalation steps, large proportion of patients treated at low (i.e. potentially sub-therapeutic) doses

• Alternate rules proposed: “2+4,” “3+3+3,” and “3+1+1” (“best of five”) rules
Accelerated Titration Designs

• 40% and 100% dose escalations
• Single patient cohorts until a dose-limiting toxicity or two moderate toxicities are observed during cycle 1 or any cycle; then revert to 3+3 design
• Reduces the number of patients who are treated at sub-therapeutic doses

Pharmacologically Guided Dose Escalation

• Assumes that dose-limiting toxicities can be predicted by plasma drug concentrations and that animal models can accurately reflect this relationship in humans
• As long as the pre-specified plasma exposure is not reached, dose escalation proceeds with one patient per dose level and typically at 100% dose increments
• Requires real time PK; difficulty in extrapolating from animal data, risk of toxicity if AUC was atypically low in the previous patient.
Continual Reassessment Method

• First Bayesian model–based method proposed in 1990

• Data from all toxicities observed during the trial are used to determine the MTD

• The occurrence of toxicity (or not) in patients enrolled at each dose level provides additional information for the statistical model and results in an adjustment of $\theta$ (which represents the slope of the dose–efficacy or dose-toxicity curve)

• Allows for rapid dose escalation

• Needs statistical support

• Concern for overdose if model incorrect
  • led to the Escalation with Overdose Control (EWOC) design
Dose-finding spreadsheet of the **modified Toxicity Probability Interval (mTPI)** method. The spreadsheet is generated based on a beta/binomial model and precalculated before a trial starts. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI. MTD, maximum-tolerated dose.
Translation of statistical designs into practice phase I trial designs

• Modeling of Bayesian adaptive designs demonstrates that more patients are treated at optimal doses compared with standard up-and-down methods

• Abstract records of 1235 cancer clinical phase I trials from the Science Citation Index database between 1991 and 2006 were evaluated along with 90 statistical studies

• Only 1.6% of the phase I cancer trials (20 of 1,235 trials) followed a design proposed in one of the statistical studies.

• All the rest followed the standard up-and-down methods

Changing Landscape of Drug Development

Increased Understanding of Cancer Biology

Advent of Targeted Therapies

High Attrition Rates/High Costs

Personalized Medicine

- Benefit + Toxicity
- No benefit + Toxicity
- No benefit No toxicity

All patients with the same diagnosis

+ Benefit

+ Toxicity

+ Benefit

+ Toxicity

- Benefit

- Toxicity

- Benefit

- Toxicity

Marx and McClure, AAV NUS GeD, 2006.55 PMDD
Development of molecularly targeted therapies

- Target is important for disease initiation or progression
- Agent modulates the target and this modulation is associated with a desired effect in preclinical models
<table>
<thead>
<tr>
<th></th>
<th>Conventional chemotherapy</th>
<th>Molecularly targeted agents</th>
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</thead>
<tbody>
<tr>
<td><strong>Cellular effects</strong></td>
<td>Cytotoxic</td>
<td>May be cytostatic</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Usually nonspecific multiple organ system; often bone marrow,</td>
<td>Presumably less toxic; target specific or off-target</td>
</tr>
<tr>
<td></td>
<td>gastrointestinal, hepatic</td>
<td></td>
</tr>
<tr>
<td><strong>Phase 1 primary end-points</strong></td>
<td>Characterize toxicities; DLT, MTD; evaluate PK</td>
<td>Determine target inhibition, OBD; evaluate PK &amp; toxicities</td>
</tr>
<tr>
<td><strong>Patient selection</strong></td>
<td>Disease histology</td>
<td>Molecular pathology or presence of target(s)</td>
</tr>
<tr>
<td><strong>Phase 2 efficacy trial end-points</strong></td>
<td>Objective tumor response (tumor shrinkage)</td>
<td>Objective tumor response or stabilization (progression-free survival)</td>
</tr>
<tr>
<td><strong>Measures of efficacy</strong></td>
<td>Anatomical imaging</td>
<td>Anatomical or functional imaging</td>
</tr>
<tr>
<td><strong>Time to clinical response</strong></td>
<td>Relatively short (e.g., 6–8 weeks)</td>
<td>Relatively late; may require prolonged dosing for therapeutic effect</td>
</tr>
</tbody>
</table>

Dose-effect curves for the antitumor and toxic effects of a MTA
Three pillars for successful transition from early phase to late phase

Exposure at the target site of action over a desired period of time

Target occupancy/binding is expected for its mode of action

Functional modulation of target

Pillar 1 and 2
Target exposure and target binding concur but no data to show relevant downstream pharmacology effect at site of action.
Risk in relying only on exposure and binding; study design & decision-making from clinical endpoint needs to be clear

Pillar 1, 2, 3
Target exposure shown and concurs with target binding which results in expression of relevant downstream pharmacology effect at site of action. PKPD well established. Maximum confidence in translation of drug exposure and pharmacology & of testing the mechanism

None or partial Pillars
Binding to target but no data to show relevant downstream pharmacology effect; exposure only in plasma, not at target site (e.g. CNS). PKPD not well established. Serious concerns that mechanism will not be tested & clinical studies unlikely to be definitive

Pillar 2 and 3
Binding to target shown but exposure only in plasma, not at target site (e.g. local administration to target); data showing relevant downstream pharmacology effect. Reasonable risk being carried forward if confident that drug reaches target in humans & clinical endpoint relevant to site of action

Designing the first-in-human trial

1. Assess target modulation
   • Directly or measure effect on a disease process
     • Possess validated PK and PD assays that accurately and reproducibly measure drug levels and allow evaluation of drug effect

2. Dose and schedule
   • Starting dose and schedule based on preclinical data
   • Incrementally increase dose-MTD or OBD?
   • Degree and duration of inhibition

3. Patient Selection-select based on presence of target
ASCO abstracts between 1991 to 2002 that included biomarkers went up from 14% to 26%, 1 out of 87 trials used biomarker as the basis for phase II dose selection.

**Biomarker:**
A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or a pharmacologic response to a therapeutic intervention.
Why are successful biomarker studies uncommon?

- **Biological heterogeneity**
  - Cellular, tumor, patient
  - Target; Tissue of interest
  - Stability
  - Day to Day variability within patient
  - Other medical conditions affecting target

- **Assay variability**
  - Within assay, between assays

- **Specimen variability**
  - Specimen handling and processing
  - Sampling procedures and amount of sample

- **Logistical and resource considerations:** Lab tests whose results are used for patient management must be validated, performed and reported by a CLIA-certified laboratory (Clinical Laboratory Improvement Amendments, Centers for Medicare & Medicaid Services (CMS))
What should be the tumor content of the biopsy?

Tumor content (%) = \( \frac{\text{Tumor area}}{\text{(Viable Tumor + Necrotic Tumor + Stroma area)}} \)

Tumor content in the biopsies: amount of minimal necrosis and stromal tissue; tumor enrichment using macrodissection.
Main reason for insufficiency is no or low tumor content, 87% (20/23) of failures and 27% (20/73) overall.

~45% of all liver biopsies were insufficient due to no or low tumor content (32% insufficiency for all tissues combined).

Two trials sample sets evaluated showed a trend in decreased tumor content in the post dose biopsy (Post dose time points were Day 6 or Day 8).

<table>
<thead>
<tr>
<th>Cause of Insufficiency Based on One Image Minimum</th>
<th>Number of Biopsies</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damaged After Collection</td>
<td>3/23</td>
<td>13%</td>
</tr>
<tr>
<td>No Tumor</td>
<td>4/23</td>
<td>17%</td>
</tr>
<tr>
<td>Low Tumor Content</td>
<td>16/23</td>
<td>70%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue of Origin</th>
<th>Insufficient Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>9</td>
</tr>
<tr>
<td>Pleural</td>
<td>1</td>
</tr>
<tr>
<td>Axilla Node</td>
<td>1</td>
</tr>
<tr>
<td>Periumbilical Node</td>
<td>2</td>
</tr>
<tr>
<td>Cervical Mass</td>
<td>3</td>
</tr>
<tr>
<td>Supraclavicular Node</td>
<td>4</td>
</tr>
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</table>

Courtesy: J Doroshow, NCI
Cryobiopsy: Freeze

Standard 18 gauge Bx

Cryobiopsy: Excise

Excisional Biopsy
Comparing Effect of 4 Tumor Harvest Methods on pAKT Levels

Separated on an 8% Tris-Gly Gel
Developing the ‘Right’ Assay Tools for Early Stage Proof of Mechanism Studies

Typical Tumor Measurements:
- Tumor Weight/Size/Regressions/Tumor Free
- Body Weight Loss/Deaths
- Optimal Activity, % T/C
- Growth Delay, % (T-C/C)

Biomarker

Genomics

Imaging

Drug Analysis

Proteomics

Metabolomics
Developing Multiplex Assays

• Require PD assays prior to clinical trials: Establish Proof-of-Mechanism
• Multiplex platforms
  - Evaluate multiple targets and downstream effectors
  - Build on successful γH2AX quantitative IFA
  - Focus on DNA damage/repair & apoptosis
• Define tissue handling, background levels, time course, calibrators
• High priority agents for NCI trials: PARPi; ATRi; XIAP inhibitors

DNA Damage/Repair Panel
UWB1.289, SN38 (1μM, 4h)

Apoptosis Panel
A375 Xenograft: 25 Mg/Kg TL32711

- DAPI
- γH2AX
- cCasp3
- γH2AX

40X Widefield + Phase

pNbs1
γH2AX
ERCC1

Merge w/o DAPI

2hr
4hr
7hr

Courtesy: Robert Kinders, PhD, Leidos-NCI
Multiplex Assays: Correlating Efficacy with MOA

HCT-116 Colon Xenograft

Similar results in HT-29 (colon) and NCI-H522 (lung) xenografts
Poly (ADP-ribose) Polymerase [PARP 1]
Temporal Effects of Single-Dose ABT-888 on PAR Levels in Colo829 Xenografts

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>1.56</th>
<th>3.13</th>
<th>6.25</th>
<th>12.5</th>
<th>25</th>
<th>TPT 15*</th>
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<tbody>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hours</td>
<td></td>
<td>18029 ± 6711</td>
<td>1361 ± 874</td>
<td>454 ± 786</td>
<td>293 ± 457</td>
<td>159 ± 319</td>
<td>143 ± 299</td>
</tr>
<tr>
<td>5% CI</td>
<td></td>
<td>10986–25072</td>
<td>444–2278</td>
<td>LLQ–1279</td>
<td>LLQ–773</td>
<td>LLQ–666</td>
<td>12150–53252</td>
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<tr>
<td>24 hours</td>
<td></td>
<td>18866 ± 5185</td>
<td>33927 ± 17651</td>
<td>11353 ± 3358</td>
<td>10404 ± 4173</td>
<td>8342 ± 7753</td>
<td>8794 ± 4957</td>
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<tr>
<td>5% CI</td>
<td></td>
<td>6070–31662</td>
<td>12010–55844</td>
<td>4062–18644</td>
<td>37–20771</td>
<td>LLQ–17969</td>
<td>LLQ–21108</td>
</tr>
</tbody>
</table>

*All doses are mg/kg. n = 6 animals per group; whole xenografts were surgically excised and half of the excised specimen was measured in the PAR immunoassay at protein loads of 10 to 20 µg per well.

Single-dose topotecan was administered by intraperitoneal injection as an additional control. Collection time points were selected to mimic the time points in the clinical trial. All units are pg PAR/mL per 100 µg protein.

TPT = topotecan; LLQ = lower limit of quantitation of the assay.

PAR levels were measured 4 h following ABT-888 administration at doses of 3 or 12.5 mg/kg as indicated (n = 6 animals/group). Values are pg PAR/mL, normalized to 100 µg protein. Solid diamond, measured point; line, linear regression fit.

Correlation of PAR levels between resected small and large tumors. The difference in scale of PAR values in vehicle compared with ABT-888 treatment groups is due to significant drug suppression of PAR.

Correlation of PAR levels between first and second quadrants dissected from resected large tumors.

Correlation of PAR levels between first and second quadrants dissected from resected small tumors.

First-in-human trial of ABT-888 in Solid Tumors

Kummar et al. J Clin Oncol 27(16); 2009
H2AX is a major effector of the ATM kinase pathway. Serine 139 phosphorylation of Histone H2AX occurs in response to double strand DNA breaks.

A) Untreated small intestine vs. testis
B) Vehicle vs. topotecan at 0.03 MTD, 0.1 MTD, and 0.32 MTD
C) Biopsy vs. skin snip with 1 MTD topotecan
D) Graph showing %NAP over time for different treatments (0.32 MTD, 0.1 MTD, and Vehicle)
Veliparib in combination with cytotoxic chemotherapy: Assessing drug target effect

Phase I Study Design – Unselected Patients in Dose Escalation followed by Specific Expansion Cohorts

Dose Escalation
- PK, Safety
- Define MTD

Cohort Expansion
- Pharmacodynamics
  - Biopsies
  - Functional imaging
- Targeted Tumor Types
  - Molecular enrichment
  - Histological enrichment
Phase I Study Design – Only Molecularly Enriched Patients

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Cohort Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamics</td>
<td>Targeted Tumor Types</td>
</tr>
</tbody>
</table>

- PK, Safety
- Define MTD

- Biopsies
- Functional imaging

- Histological enrichment
Biomarkers: regulatory definitions

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

**Integral**
- Used for patient selection
- Used to determine patient treatment
- Performed in CLIA environment
- e.g. mutBRaf(V600) with BRaf inhibitor (dabrafinib, vemurafinib)

**Integrated**
- Used for patient description
- Provide evidence of pathway activation
- Pharmacodynamic
- CLIA ready
- e.g. study of biomarkers for Ras/Raf/MEK signaling

**Exploratory**
- Descriptive
- Not validated or fit-for-purpose
- e.g. study of cross talk between Ras/Raf/MEK and PI3K signaling cascades

BEST (Biomarkers, EndpointS, and other Tools) Resource
Fit-for-Purpose:
Parallel Drug and Biomarker Development

**Exploratory Method Validation**

Pre-validation

**Advanced Method Validation**

In-study Method Validation

**Method Validation**

- Discovery/Pre-clinical
- Phase 0
- Phase 1
- Phase 2
- Phase 3
- Post-Marketing

**Investigational Drug Development**

- Assay Analytic Validation
- Intended Use (GCLP)
- Clinical Utility (CLIA)
- Reproducibility, Validity, Variability
- Validation Biomarker Selective

**Diagnostic Biomarker Development**
Definitions

• **Analytical performance (analytical validity):** how accurately the test detects the analyte(s) of interest

• **Clinical Validity:** How well does the assay result correlate with outcome?

• **Clinical Utility:** How does use of the assay improve outcome?
Challenges in developing drug combinations

• **Dose adjustments required for overlapping toxicities: is the dose still resulting in adequate exposure?**

• Lack of preclinical models of combination therapy
  • No standard, combinatorial high-throughput screening models to examine combinations in vitro;
  • no in vivo models standardized for use with targeted combinations;
  • and lack of approved or investigational agents available for preclinical evaluation

• Inability to assess target effects clinically. That is, lack of assays or imaging tools, and lack of assay standardization

• Inadequate clinical trials methodology for combination studies
  • Need to screen large numbers of patients for specific mutations?
  • Need for tumor biopsies? Relevance of histological versus genetic homogeneity?
  • Pharmacokinetic interactions? Relevant end points for trials — response versus lack of disease progression?

• Intellectual property challenges to combining agents from competing sponsors

• Regulatory framework for the commercialization of targeted combinations
Dose is context dependent: Patient Selection
### Declining costs of sequencing: massively parallel next-generation sequencing and subsequent computational analysis

<table>
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<tr>
<th>Date</th>
<th>Cost per Mb</th>
<th>Cost per Genome</th>
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<tr>
<td>Jul-14</td>
<td>$0.05</td>
<td>$3,905</td>
</tr>
</tbody>
</table>
COSMIC: Catalog of Somatic Mutations in Cancer

• COSMIC launched in 2004, detailed 4 cancer genes
• 2014: world's largest and most comprehensive resource
  • 2,002,811 coding point mutations in over one million tumor samples
  • 6 million noncoding mutations,
  • 10,534 gene fusions,
  • 61,299 genome rearrangements
  • 695,504 abnormal copy number
  • segments and
  • 60,119,787 abnormal expression variants

Transition From Histology $\rightarrow$ Genomic Driver Mutations

Targeting mutations works!!

Vemurafenib in melanoma harboring activating mutations (T→A transversion at position 1799) in B-RAF (V600)

RR (6%CR, 47% PR); PFS 6.8 mos

Sosman J, et al. NEJM 2012;366:8
Incorporating Molecular Profiling into Early Phase Trials

• Targeting driver mutations; enrichment strategies
  • Phase I for Crizotinib – standard dose escalation in solid tumors, 2 pts responded → profiling showed ALK rearrangement → protocol amended to include an expansion cohort → 1500 patients screened from August 2008 through February 2010 to enroll 82 patients with FISH+ ALK rearrangement → 57% objective confirmed partial/complete response
  • No statistically predetermined enrollment goal for ALK-positive patients was established.
  • August 26, 2011: Crizotinib received accelerated approval by the FDA along with a companion diagnostic (Vysis ALK Break Apart FISH Probe Kit)

A. Single-Drug

Patients with tumors at multiple primary sites and/or of multiple histologic types

Screen with tumor mutation panel

Patients with actionable mutations are assigned test drug

Patients with nonactionable mutations leave study

Simon R. Ann Int Med 2016; 165:270
Vemurafenib Basket Trial

NSCLC  RR 42%
LCH    RR 43%

Umbrella Trials

B. Multiple-Drug

Patients with tumors at multiple body sites and/or of multiple histologic types

Screen with tumor mutation panel

Patients with actionable mutations are triaged to the appropriate test drug (based on target)

Patients with nonactionable mutations leave study

Simon R. Ann Int Med 2016; 165:270
Phase I trials sit at the interface of laboratory advances and later stage clinical care; expedite development of new treatments; basis to prioritize resource allocation.

**Phase I**
- First-in-human trials; Safety and tolerability; Dose
- Across tumor types
- How much to give and how? Does it work? Who benefits?
- 50-100 patients

**Phase II**
- Determine clinical benefit in patients with a type of cancer
- One type of cancer or cancers that share a common trait?
- 100-200 patients

**Phase III**
- Compare to existing standard of care
- Does it work better than what is already out there for a given cancer or subset of multiple cancers?
- 600-800 patients

**Phase IV**
- Post-marketing safety studies
- Is it safe and effective in large populations?
- 1000s of patients

6-7 years
Future Considerations

- **Early phase trials** (including FIH) will need to be designed to address key questions
  - Target modulation; PK/PD relationships
  - Duration and degree of modulation
  - Sequencing of drugs in combination

- **Establish RP2D**
  - Safe and Tolerable
    - ‘good’ normal tissue tolerability
    - Cumulative toxicities should be tolerable, not just first cycle DLTs
  - Has optimal antitumor effect
    - How does this correlate with target inhibition?
    - Need to define the desired level of target inhibition needed to achieve the antitumor effect

- **Proof-of-mechanism** (did you hit the target?) and **proof-of-concept** (did hitting the target affect growth-controlling pathways?)

- Understanding relationship between dose, schedule, target inhibition, and efficacy: essential for developing combinations
Clinical Translational Research and Cancer Biology: Bedside to Bench and Back

**Clinical observations:**
- Clinical response
- PK
- Functional imaging
- Tumor and normal tissue PD markers
- CTCs, CECs
- Tumor-initiating cells

**Patients eligible for early phase clinical trials**

**Analysis of tumor and Other tissues for pathway activation or biomarker**

**Patient assigned to trial Based on molecular characterization of tumor**

**Patient monitoring**

**Patient monitoring:** Post-treatment molecular re-analysis for response/resistance

**Non-clinical models for targets**

**Translational research with clinical models**
- Sequencing
- Methylation
- FISH
- IHC
- Expression array
Standard Drug Development Pipeline: Re-envisioned

GOAL:

Drugs

Assays

Trials

Hypothesis Generation

Clinical Candidate Development

Commercialization

Time: 5-6 Years

Time: 10-12 Years

GOAL:

$2000 MM

Cumulative Investment

$500-600 MM

$200-300 MM

$20-60 MM

Target/Molecule Discovery

Target Validation

Assay Development

Lead Optimization

Preclinical Development

Phase I

Phase II

Phase III

Registration

Global Launch

Global Optimization

Risk