Evolution of Early Phase Trials:
Clinical Trial Design in the Modern Era

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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
Toxicity driven dosing: Hypothetical dose-response and dose-toxicity (DLT) curves

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; accelerated titration 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)
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
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
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 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

Considerations for conducting biomarker studies

• 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))
Veliparib in combination with cytotoxic chemotherapy: Assessing drug target effect

Phase I Study Design – Unselected Patients (or molecularly enriched population) in Dose Escalation followed by Specific Expansion Cohorts

**Dose Escalation**

- **Pharmacodynamics**
  - **Targeted Tumor Types**
    - PK, Safety
    - Define MTD
    - Biopsies
    - Functional imaging
    - Molecular enrichment
    - Histological enrichment

Define the degree and duration of target inhibition to establish optimal biologic dose and schedule. Dose-PK-PD relationship important to inform dose and schedule of drug combinations.
Patient Selection: Transition From Histology \(\rightarrow\) Genomic Driver Mutations

BASKET Trials

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
Efficacy of larotrectinib in TRK fusion cancers

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
Considerations in designing MP driven trials

• Is the molecular aberration a ‘driver’? Does it have a functional consequence?
• Treatment decisions: target driven or histology driven?
  • Importance of target may be disease context dependent
• What should be the tumor content of the biopsy? How many biopsies need to be analyzed?
• How many cells need to carry the mutation of interest?
• Single vs multiple aberrations?
• Efficacy of the agent
Shift in the Clinical Trial Paradigm: Development of Checkpoint inhibitors

- December 2010: First-in-human trial of Pembrolizumab IND submitted
  - 3+3 design, dose levels: 1, 3, 10 mg/kg; total of 10 pts in dose escalation, 20 pts in dose expansions at different dose levels
  - Over 2.5 yrs, 8 amendments, 9 distinct expansion cohorts - total accrual ~1,100 pts
  - 173 pts with melanoma previously treated with ipilimumab, enrolled on expansion cohort B2, randomized, dose comparative cohort - 26% RR
- September 2014: Accelerated approval by the FDA for melanoma
- October 2015: Data from this trial supported FDA approval for NSCLC

How is the decision made to keep enrolling?

• Who decides? Based on what information?
  
  • “The Sponsor will make internal assessment based on observed efficacy results from the initial 20 subjects as well as efficacy results of [standard of care] at the time for each individual tumor type to make the decision whether to expand to 60 subjects. Since it's not based on one single efficacy endpoint and we need the flexibility to look at totality of efficacy data, we choose not to formally put decision criteria in the protocol.”
  
  • Not all agents will have the same successes as the “breakthrough” approvals of nivolumab and pembrolizumab
  
  • Studies cannot be designed to presume success: *studies need to be designed to protect patients from failures.*

Courtesy: Dan Sargent, Mayo Clinic
# Trends in Clinical Trial Protocol Complexity

<table>
<thead>
<tr>
<th></th>
<th>2000-2003</th>
<th>2008-2011</th>
<th>Increase in Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Procedures per Trial Protocol (median) (eg, bloodwork, routine exams, x-rays)</td>
<td>105.9</td>
<td>166.6</td>
<td>57%</td>
</tr>
<tr>
<td>Total Investigative Site Work Burden (median units)</td>
<td>28.9</td>
<td>47.5</td>
<td>64%</td>
</tr>
<tr>
<td>Total Eligibility Criteria</td>
<td>31</td>
<td>46</td>
<td>48%</td>
</tr>
<tr>
<td>Clinical Trial Treatment Period (median days)*</td>
<td>140</td>
<td>175</td>
<td>25%</td>
</tr>
<tr>
<td>Number of Case Report Form Pages per Protocol (median)</td>
<td>55</td>
<td>171</td>
<td>211%</td>
</tr>
</tbody>
</table>

*These numbers reflect the “treatment duration” of the protocol only.

http://chartpack.phrma.org/2016-perspective/chapter-2/the-complexity-of-clinical-trials-has-increased
Design of Large First-in-Human Cancer Trials

- Is there a compelling rationale for including multiple expansion cohorts?
- Is the sample-size range consistent with the stated objectives and end points?
- Is there an appropriate statistical analysis plan for all the stated end points?
- Are the eligibility criteria appropriately tailored to the expansion cohorts?
- Is there a defined end to the trial, in terms of both efficacy and futility?
- Is there a system in place to communicate with all investigators in a timely fashion?
- Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
- If the trial may be used for regulatory approval, is there an independent oversight committee?
- If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

What do we want to achieve at the end of an early phase trial?

- Determine Dose
  - Defining DLTs: Used to be first cycle and then toxicities had to recover to grade 1/baseline prior to re-initiating treatment at the next lower dose
- For immunotherapies:
  - May not occur in the first cycle
  - Take weeks to resolve
  - Not dose related
  - Can we safely continue the patient on treatment following resolution of toxicity?
- Antitumor activity (hint of activity)

Adverse events associated with IO agents
Determining Antitumor Activity

- RECIST 1.1, iRECIST, irRECIST, imRECIST
- Pseudoprogression (PP) as an increase in the size of lesions, or the visualization of new lesions, followed by a response, which might be durable. Need for confirmatory scans

24/655 (7%) pts in KEYNOTE-001 melanoma trial of pembrolizumab (J Clin Oncol 2016 (34))
Other solid tumors: PP 2%. J Clin Oncol 34 (15)suppl (May 2016) 6580
Evolution of early phase trials

- Establishment of MTD - Cytotoxic Chemotherapies
- Target modulation; Establishing the ‘Optimal Biologic Dose’ - Targeted Agents
- “Concept of driver mutations” - Basket/umbrella trials
- “Seamless drug development” - Early phase trials with multiple expansion cohorts: Immunotherapies
- Intersection of target modulation, molecular profiling, immunotherapy in early phase trials
Stages of Clinical Research—Reinvented

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

6-7 years