Phase 0 Clinical Trials

Sponsored by
Center for Cancer Research
National Cancer Institute
Slides courtesy of:
James, Doroshow, MD
Director, Division of Cancer Treatment and Diagnosis
National Cancer Institute

What is a Phase 0 trial?

- First-In-Human trial:
  - Limited number of subjects (≈10-12)
  - Very limited drug exposure
    - Low, supposedly non-toxic doses
    - Limited duration of dosing (≤ 7 days)
  - One course
  - No therapeutic (or diagnostic) intent
  - Conducted prior to traditional Phase 1 dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program
  - Can be initiated with a less extensive pre-clinical data than traditional Phase 1 trials
- Also referred to as:
  - Pre-phase 1 trial
  - Pilot study
  - Exploratory Investigational New Drug (IND) study

Goals of a Phase 0 Trial

Generate data to:
- Inform subsequent development of the agent
- Enhance efficiency of subsequent development of the agent
- Increase chance of success of subsequent development of the agent

Why are Phase 0 Oncology Trials Needed?

- There’s a need to improve the efficiency and success rate of clinical trials
- Most drugs in clinical development do not make it to registration
- Failure rate is higher for oncology drugs than other indications
- Most drugs that fail, fail in late stages of clinical development
- Late failure (due to bad drug or target) means wasted resources, including patients

Success Rates from First-in-Man to Registration

Data from 10 biggest drug companies from 1991-2000

Kola And Landis; Nature Reviews Drug Discovery 2004

Most drugs fail in late stages of development...particularly in Oncology

70% of oncology drugs that enter Phase 2 fail to enter Phase 3
59% of oncology drugs that enter Phase 3 fail
Risk of failure may be higher for novel targeted agents

Kola & Landis; Nature Reviews Drug Discovery 2004
Why drugs fail

• Unfavorable PK currently plays less of a role compared to early 1990’s
• Lack of efficacy continues to play a major role
• Lack of predictive animal models


How can Phase 0 trials improve efficiency and success of subsequent trials?

• Eliminate an agent very early in clinical development because of poor PD (pharmacodynamic) or PK (pharmacokinetic) properties
  • E.g., lack of target effect, poor bioavailability, rapid clearance
• Inform subsequent trials by:
  • Validating a PD assay for assessing target modulation
  • Developing a reliable SOP for tissue acquisition, handling, and processing
  • Determining dose and time course that yields a required target effect
  • Intensively evaluating PK, providing a closer approximation to a safe, but potentially effective starting dose and support for limited sampling in subsequent trials

Phase 0 Trial Outcomes...

• Determine whether a mechanism of action defined in non-clinical models can be observed in humans (e.g., binds to or inhibits its alleged target)
• Provide human PK/PD data for an agent prior to definitive Phase 1-2 testing
• Refine biomarker assay using human tumor tissue and/or surrogate tissue

... Phase 0 Trial Outcomes

• Evaluate human PD and/or PK (e.g., bioavailability) of two or more analogs directed at the same target and possessing practically the same properties in vitro and in animal models, helping to select the most promising candidate for further development
• Evaluate in humans an agent’s biodistribution, binding characteristics and target effects using “micro-dosing” and a variety of novel imaging technologies

Prioritizing Candidate Agents for Phase 0 Study

• PD endpoint is critical to development (need credentialed PD marker or drug target)
• Pre-clinical data show a wide therapeutic window
• PD modulation expected at low doses and short durations of exposure (e.g., ≤7 days)
• Drug target effect likely to be determined with a relatively small sample size (=10-15 patients)
• Need for bioavailability or PD data to select best candidate among two or more analogues

What does a Phase 0 trial involve...

• Pre-clinical: Studies in animal models prior to initiating Phase 0 trial to:
  • Validate PD biomarker assay
  • Simulate human tissue acquisition, handling and processing
  • Demonstrate drug effect on target or biomarker
  • Determine PK-PD relationships
  • Evaluate drug biodistribution and binding using imaging technologies
• Validate PD assay methodology using human tumor samples or surrogate tissue (e.g., PBMCs) prior to Phase 0 trial
...What does a Phase 0 trial involve

Pre-Clinical → Clinical
- Interrogating and validating target or biomarker assay in human tumor biopsies and/or surrogate tissue
  - Reproducibility - across technicians, labs
  - Variables/conditions - standards, temperature, storage, dilution effects (linearity?)
  - Coefficient of variability (needs to be tight)
- Developing an SOP for human tissue acquisition, handling and processing
- Demonstrating drug target or biomarker effect
- Determining PK-PD relationships
- Drug biodistribution and binding using novel imaging technologies
- Innovative statistical designs
  - Limited sample size
  - PD and PK as primary endpoints, rather than MTD

Phase 0 Statistical Issues
- Limit sample size to 6-15 patients, generally
- Define primary endpoint(s) prospectively
- If possible, obtain a measure of intra-patient variability for the pre-treatment endpoint values
- Define thresholds (binomial) for declaring treatment effect on biomarker (efficacy) for an individual patient, for a given dose, based on both biological and statistical criteria (5% false +)
- Target a reasonable efficacy % threshold, across patients, at a dose level, for detection with high power (90%)
- Maintain a reasonable false positive rate (10%) across dose levels

Phase 0 Program: Logistical Considerations...
- Mechanism for selecting and prioritizing candidate agents
- Dedicated non-clinical PD assay development laboratory including non-clinical animal models
- Dedicated human tissue PD laboratory, capable of real-time analysis
- PK lab capable of real-time analysis
- Clinical team with expertise in conduct of early phase trials

...Phase 0 Program: Logistical Considerations
- Efficiently integrated collaborations between the clinical research team and:
  - PK and PD laboratory scientists
  - Biospecimen procurement and processing staff
  - Interventional radiologists
  - Special imaging and nuclear medicine staff
  - Statisticians
  - Regulatory bodies
  - Drug sponsors
  - Project Managers
- Willing patient participants

Phase 0 Program: Ethical Considerations
- Potential barriers to enrollment
  - No therapeutic intent or chance of benefit
  - Pre- and post-treatment tissue biopsies
  - Delay or exclusion from other trials or therapies
- External concerns about ethics and availability of patients for study
- Institutional Ethics committee review and input
- Informed Consent Process
  - Need to clearly explain the rationale for the study
  - Need to define the limited treatment and follow up period
  - Need to clearly state that there is absolutely no anticipated clinical benefit to the participant

Some Measures of Success Phase 0
- Promising candidate drugs are identified and prioritized early
- Less promising drugs are eliminated early in development
- Efficiency and success rate of Phase 1-2 trials are improved
- Less drugs fail in late stages of clinical development
- Higher proportion of drugs in clinical development make it to registration and FDA approval
- Resources shifted to Phase 0 conserve resources in subsequent development, including highly valued patient participation
References


Evaluation

Please complete the evaluation form and fax to Elizabeth Ness at 301-496-9020.

For questions, please contact Elizabeth Ness 301-451-2179 nesse@mail.nih.gov