Phase 0 Clinical Trials

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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

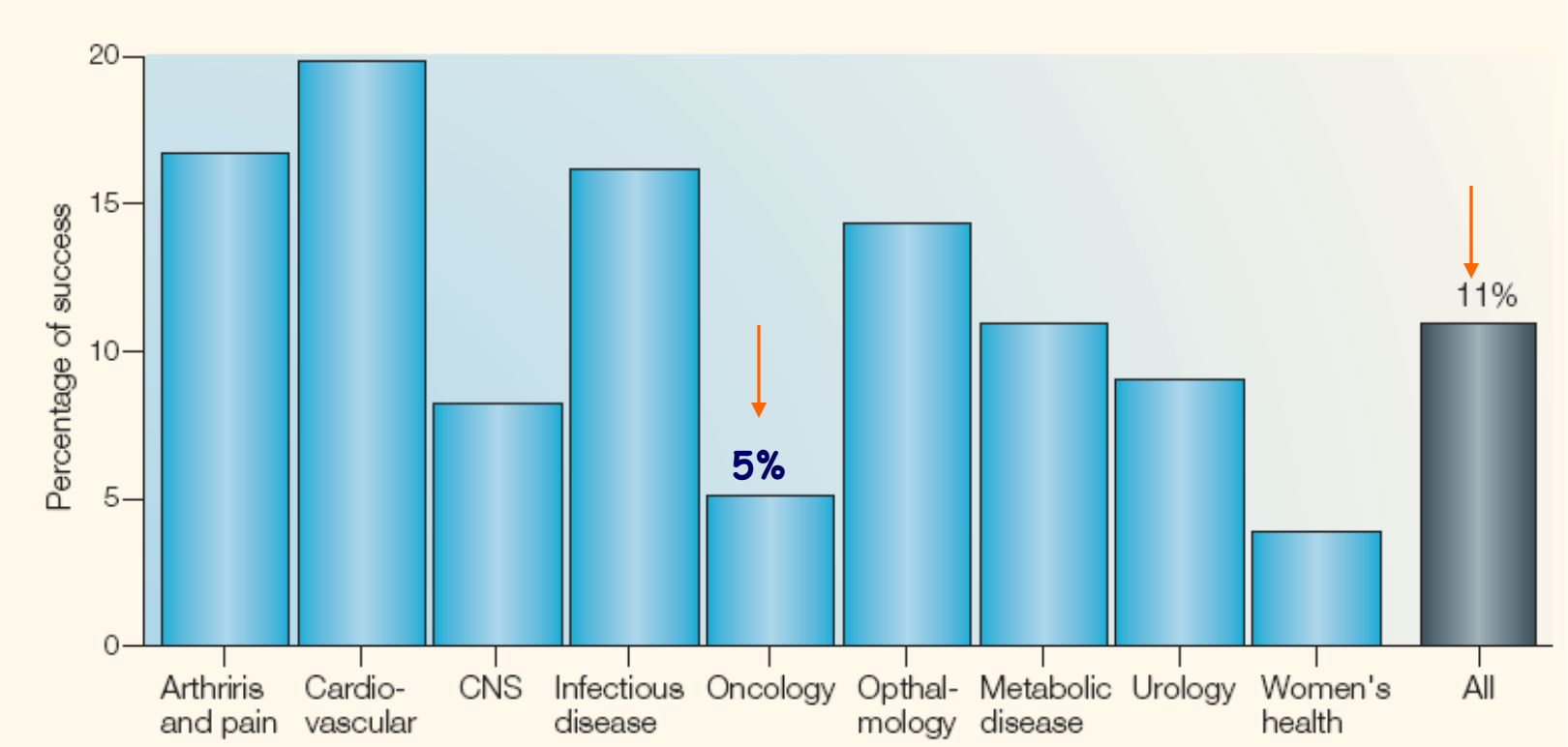
Generate data to:

- 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

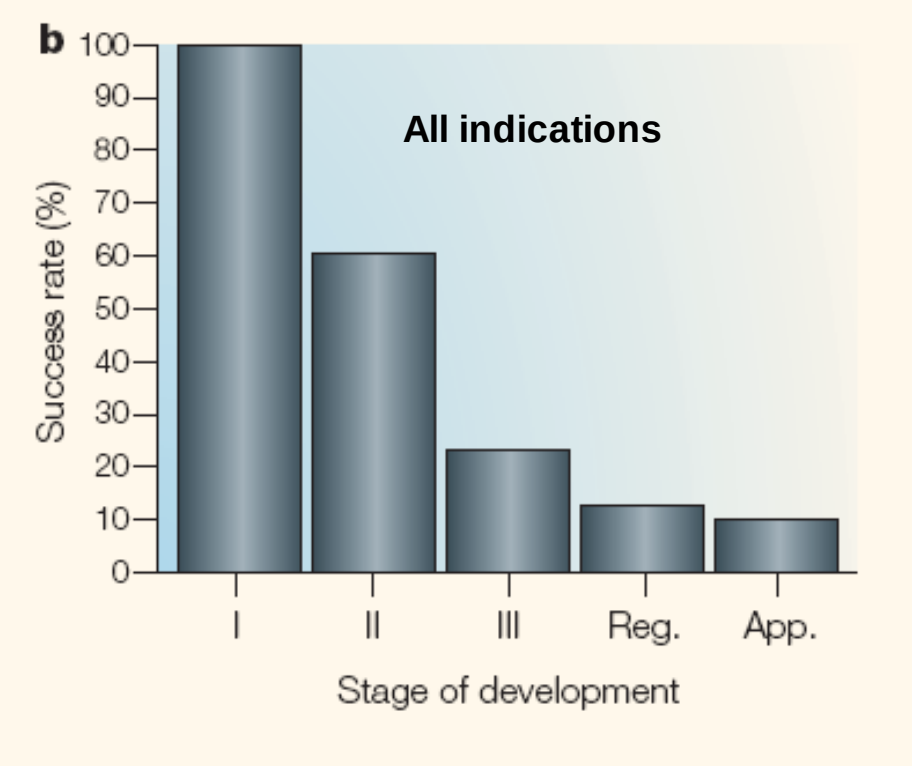


Data from 10 biggest drug companies from 1991-2000

Kola And Landis; Nature Reviews Drug Discovery 2004

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

Rates of success for compounds entering first in man that progress to subsequent phase



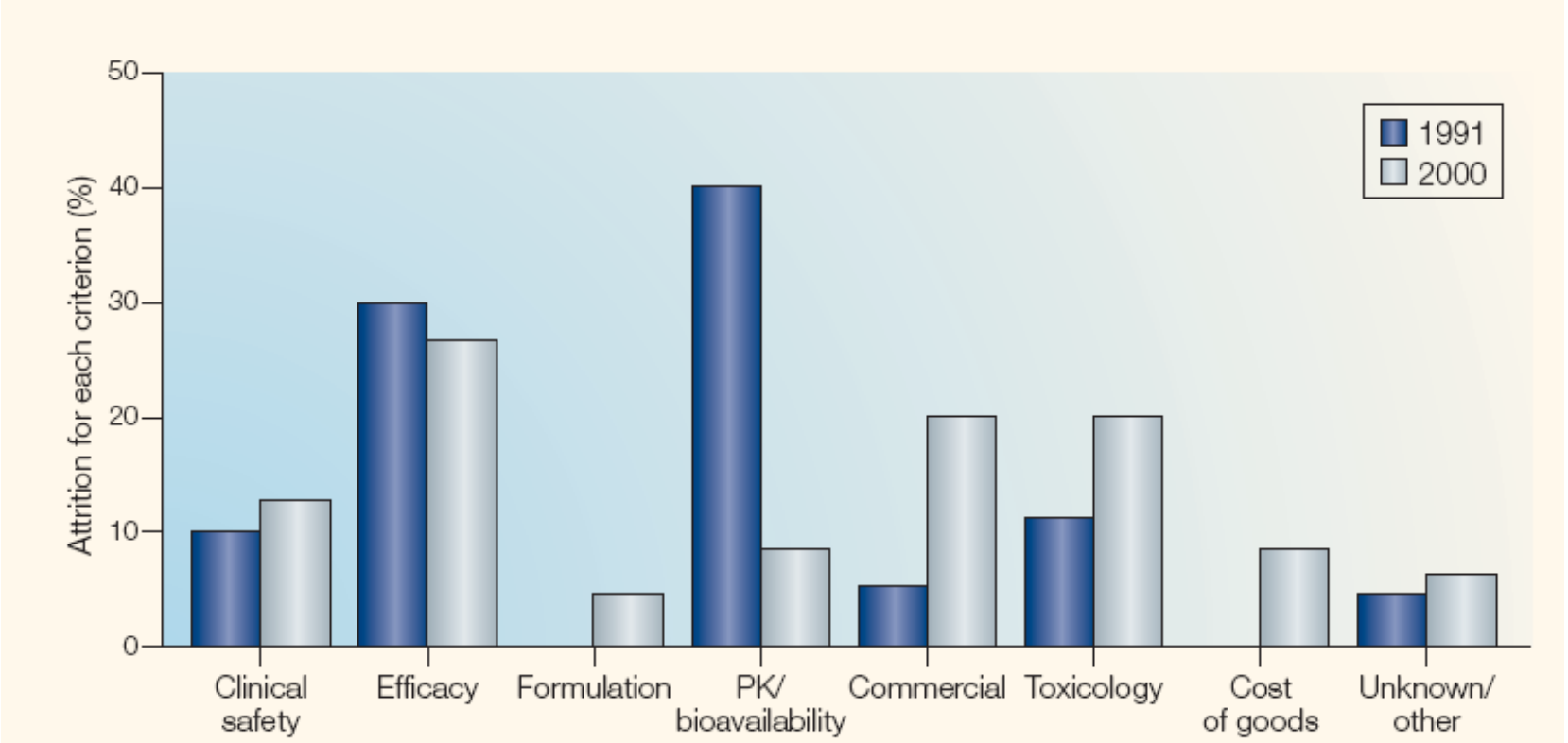
70% of oncology drugs that enter Phase 2 fail to enter Phase 3

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

Kola & Landis; Nature Reviews Drug Discovery 2004, Ma & Zemmel; Nature Reviews Drug Discovery 2002

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…

- Kola, I. & Landis, J. (2004). OPINION: Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery, 3*, 711-716.

- Ma, P. & Zemmel, R. (2002). Value of novelty *Nature Reviews Drug Discovery, 1 (8)*, 571-572.

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