Phase 'O' Clinical Trials in Cancer Drug Development: From Concept to Practice

James H. Doroshow, M.D.
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Types of Phase 0 Trials

- 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 human biodistribution and binding characteristics using "micro-dosing" and supersensitive analytical techniques.

- Development of novel imaging probes.

- Determine whether a mechanism of action defined in non-clinical models can be observed in humans (e.g., drug binds to or inhibits its alleged target) while simultaneously refining a biomarker assay using human tumor tissue and/or surrogate tissue.
### Differences Between Phase 0 & Phase I Trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phase I Trial</th>
<th>Phase 0 Trial</th>
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<tbody>
<tr>
<td>Primary Endpoint</td>
<td>Establish MTD</td>
<td>Target modulation or ability to image target</td>
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<tr>
<td>Dose Escalation</td>
<td>Determine safety/toxicity</td>
<td>Achieve desired exposure or target modulation, enable dose selection for future studies</td>
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<tr>
<td>Preclinical Biomarker Studies</td>
<td>Not consistently performed before trial</td>
<td>Required to have pre-clinical PK and PD assay development and qualification before initiation of trial</td>
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<tr>
<td>Biomarker Assays</td>
<td>Not consistently performed. Most Phase I trials do not emphasize PD markers</td>
<td>Biomarker assays and/or imaging studies are integrated to establish MOA in patient samples</td>
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How Can Phase 0 Trials Improve Efficiency and Success of Subsequent Trials?

- Eliminating an agent very early in clinical development because of poor PD or PK properties
  - E.g., lack of target effect, poor bioavail., rapid clearance
  - “Fail Fast, Fail Early”

- By informing subsequent trials
  - 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
What Does a Phase 0 Trial Involve?

Pre-Clinical to Clinical Transition

- Assay development in vitro and in vivo
- Development of pre-clinical system on which to model tissue acquisition, handling, and processing
- Demonstration of drug target or biomarker effect and PK-PD relationships in vivo
- Drug biodistribution and binding using novel imaging technologies
- Innovative statistical designs
  - Limited sample size
  - PD and PK as primary endpoints, rather than MTD
Typical Rodent Tumor Sample Collection Methods

- Euthanasia
- Tumor resection
- Transfer to tube
- Freeze in dry ice
- Removal of tumor not perceived as crucial
- Tumor size, handling, acquisition method seldom considered in preparation for clinical trial
Cryobiopsy: Freeze

Standard 18 gauge Bx

Cryobiopsy: Excise

Excisional Biopsy
Comparing Effect of Four Tumor Harvest Methods on pAKT Levels
Integrated Phase 0 Research Team

REGULATORY AGENCY

IND Sponsor
• National Cancer Institute
• Pharmaceutical Industry
• Investigator

CLINICAL

Trial Monitor

Review imaging studies to determine feasibility of obtaining biopsies
Schedule tumor biopsies: coordinate with times for drug administration

LABORATORY

Drug Development Clinic

Medical Oncologists
Research Nursing
Clinical Nursing
Data Managers
Social Workers

Pathology Laboratory

Laboratory for Tissue Handling and Processing

Laboratory for Pharmacodynamic Analysis

Repository

Patient Education

Documentation of patient understanding of the nature of the clinical trials

Research Imaging

Interventional Radiology

Bioethics

Research Nursing

Medical Oncologists

Clinical Nursing

Data Managers

Social Workers
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 Trials - Ethical Considerations

Ethical Issues (they are challenging, but not insurmountable)

- Potential barriers to enrollment
  - No therapeutic intent or chance of benefit; but low risk
  - Pre- and post-treatment tissue biopsies
  - Delay or exclusion from other trials or therapies; can be avoided

- External concerns about ethics and availability of patients for study

- Institutional Ethics committee review and input

- IRB approval

- 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 and document that there is absolutely no anticipated clinical benefit to the participant
Poly (ADP-Ribose) Polymerase (PARP)
Phase 0 at NCI

- First Phase 0 oncology trial
- IND filed with FDA May 12, 2006 and allowed to proceed June 15, 2006
- "A phase 0 pharmacokinetic, pharmacodynamic study of ABT-888, an inhibitor of poly (ADP-ribose) polymerase (PARP), in refractory solid tumors and lymphoid malignancies"
Objectives

**Primary:**

- Determine a non-toxic dose range at which ABT-888 inhibits PARP in tumor samples and in peripheral blood mononuclear cells (PBMCs)
- Determine the pharmacokinetics of ABT-888
- Determine the time course of PARP inhibition in PBMCs by ABT-888

**Secondary:**

- Determine the safety of administering one dose of ABT-888
Tumor biopsies planned:

- Significant PARP inhibition in PBMCs from at least 1 of the 3 participants at a given dose level, OR
- Plasma $C_{\text{Max}}$ of 210 nM was achieved in at least 1 participant
The objective of dose escalation is to investigate a PD end-point, *i.e.* inhibition of PARP activity and **not** to determine the MTD.

Dose escalation continued with the goal to achieve significant PARP inhibition in tumor samples in 3 out of 3 participants at 2 dose levels.
Trial Results (To Date)

- 13 patients enrolled on study, 11 are evaluable
- 3 patients (10 mg); 3 patients (25 mg); 7 patients (50 mg; 2 NE: tumor biopsy negative for PAR levels at baseline (1), 1 pt withdrew prior to receiving drug due to personal reasons)
- Age (range): 49-74 years
- Diagnoses: carcinoid (1), colorectal cancer (3), small cell lung cancer (1), low grade lymphomas (3), CTCL (3), adenocarcinoma of the external auditory canal (1), SCC head and neck (1)
- Patients monitored by serial bloodwork, EKGs, physical exams
Mean (n = 3 per dose level) Plasma Concentrations of ABT-888 Following a Single Oral Dose

- 10 mg dose
- 25 mg dose
- 50 mg dose
- 0.21 uM target
PAR Inhibition in PBMCs

Cohort 1

Cohort 2

Cohort 3

Percent of Baseline

Baseline 2 hrs 4 hrs 7 hrs 24 hrs

Percent of Baseline

Baseline 2 hrs 4 hrs 7 hrs 24 hrs

Percent of Baseline

Baseline 2 hrs 4 hrs 7 hrs 24 hrs

Legend:
- Pt 1
- Pt 2
- Pt 3
- Pt 4
- Pt 6
- Pt 7
- Pt 8
- Pt 10
PAR Inhibition in Tumor Biopsies

![Graph showing PAR inhibition in tumor biopsies from different patients.](image-url)
At the 50-mg dose level, 2 additional patients underwent a tumor biopsy at 24 hours post ABT-888 administration to evaluate time to recovery of PARP activity.
First Phase 0 – Where Are We Now?

- Established that ABT-888 inhibits the target of interest at clinically achievable concentrations using an assay validated in preclinical models using clinical procedures
- Established target assay feasibility in human samples after qualification in animal models
- Developed SOPs for human tissue acquisition, handling and processing
- Performed real-time PK and PD analyses (results received within 72 hours of obtaining sample)
- PK and PD data, including timing of tumor and PBMC sampling, available well before planned Phase 1 combination studies; PBMCs as surrogate
- Not “just another clinical trial”; resources, logistics, and multidisciplinary team crucial
First Phase 0 Trial - Timeline

- First Patient in Clinic: (Jun 13, 2006)
- 1st Cohort Completed: (July 25, 2006)
- 2nd Cohort Completed: (Oct 25, 2006)
- Concept Approval: (Dec 1, 2005)
- Exp IND accepted by FDA: (May 12, 2006)
- Phase 1 Combination Trials: (June, 2007)
When Will Phase '0' Trials Be Helpful?

Consider Phase '0'

- Targeted drug with wide therapeutic index
- Developed for chronic or multi-dose oral administration
- Require clinical pharmacodynamic marker development for further studies
- Imaging agent with or without therapeutic

NOT Phase '0' Appropriate

- Cytotoxic agent with very narrow therapeutic index
- Agent to be used on iv intermittent schedule
Models of Cancer Drug Development: Present and Future
### NCI Phase '0' Team

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<th>CCR</th>
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<tr>
<td>Joseph E. Tomaszewski</td>
<td>Shivaani Kummar</td>
<td>Ray Klecker</td>
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<td>Jerry Collins</td>
<td>Martin Gutierrez</td>
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<td>Tony Murgo</td>
<td>Robert Wiltrout</td>
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<tr>
<td>Jennifer Low</td>
<td>Lee Helman</td>
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<tr>
<td>Oxana Pickeral</td>
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<tr>
<td>Melinda Hollingshead</td>
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<tr>
<td>Gurmeet Kaur</td>
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<tr>
<td>Sherry Yang</td>
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<tr>
<td>Larry Phillips</td>
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<tr>
<td>Larry Rubinstein</td>
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<td>Seth Steinberg</td>
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<tr>
<td>Barbara Mroczkowski</td>
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| NCI Frederick                 |                              |                              |
| Ralph Parchment               |                              |                              |
| Robert Kinders                |                              |                              |
| Jay Ji                        |                              |                              |
| Yiping Zhang                  |                              |                              |
| Tiziano DiPaolo               |                              |                              |
| William Jacob                 |                              |                              |
| Vali Sevastita                |                              |                              |
| Melanie Simpson               |                              |                              |
| and numerous technical        |                              |                              |
| support staff                 |                              |                              |