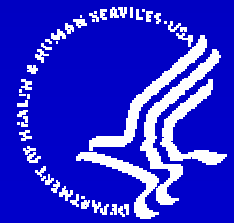


Phase '0' Clinical Trials in Cancer Drug Development: From Concept to Practice

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

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

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

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

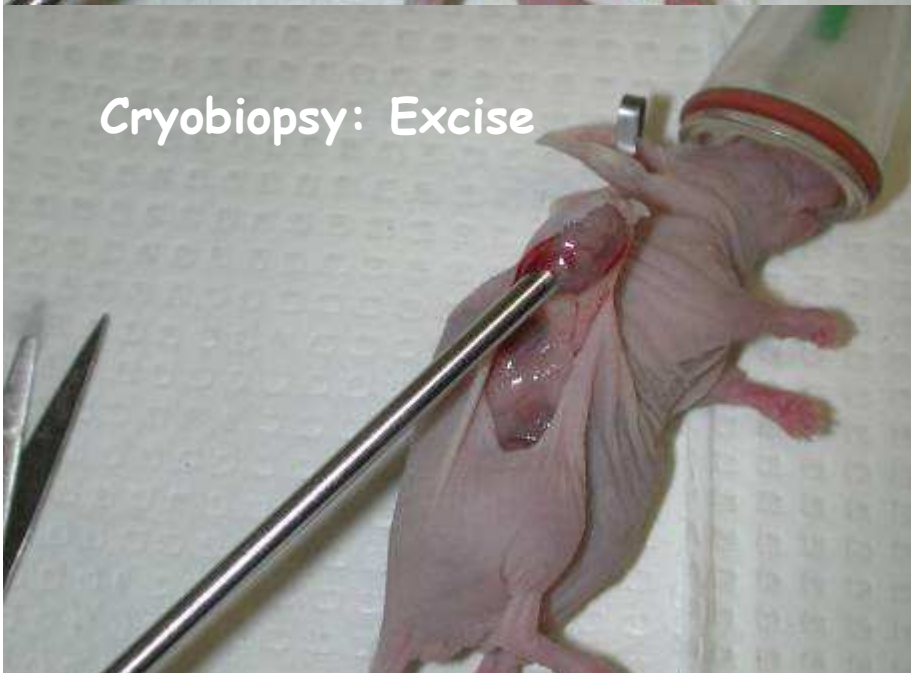
Standard 18 gauge Bx



Cryobiopsy: Freeze



Cryobiopsy: Excise

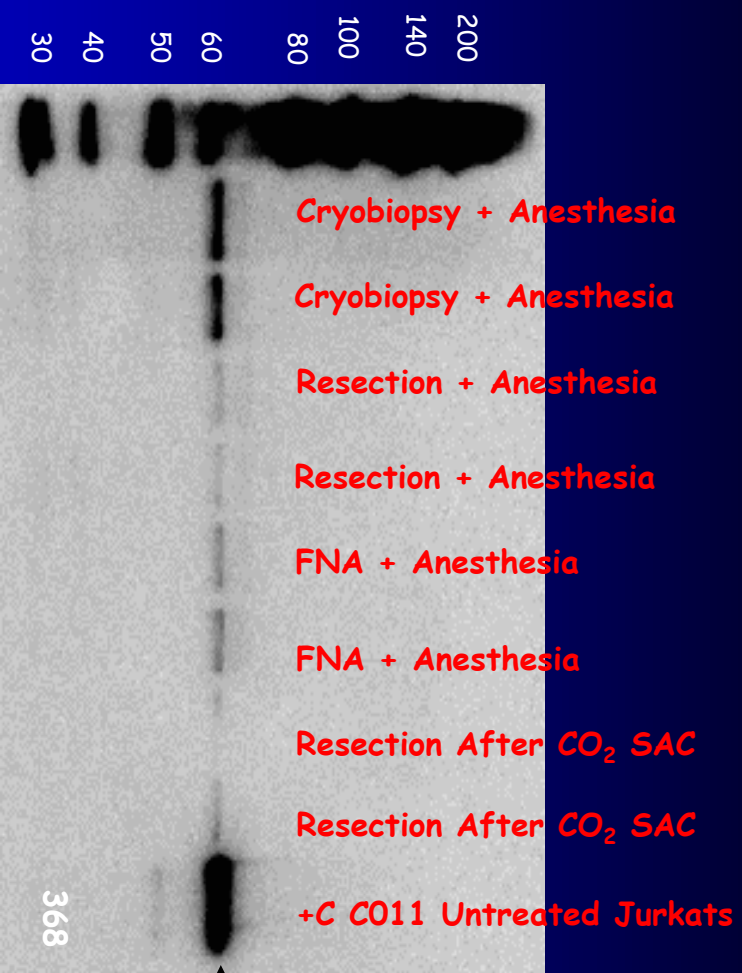


Excisional Biopsy



Comparing Effect of Four Tumor Harvest Methods on pAKT Levels

phospho-AKT
(Cell Signaling #9271)



60 kDa

PAKT Settings
Min 20.0
Max 75.0
1 min exp.

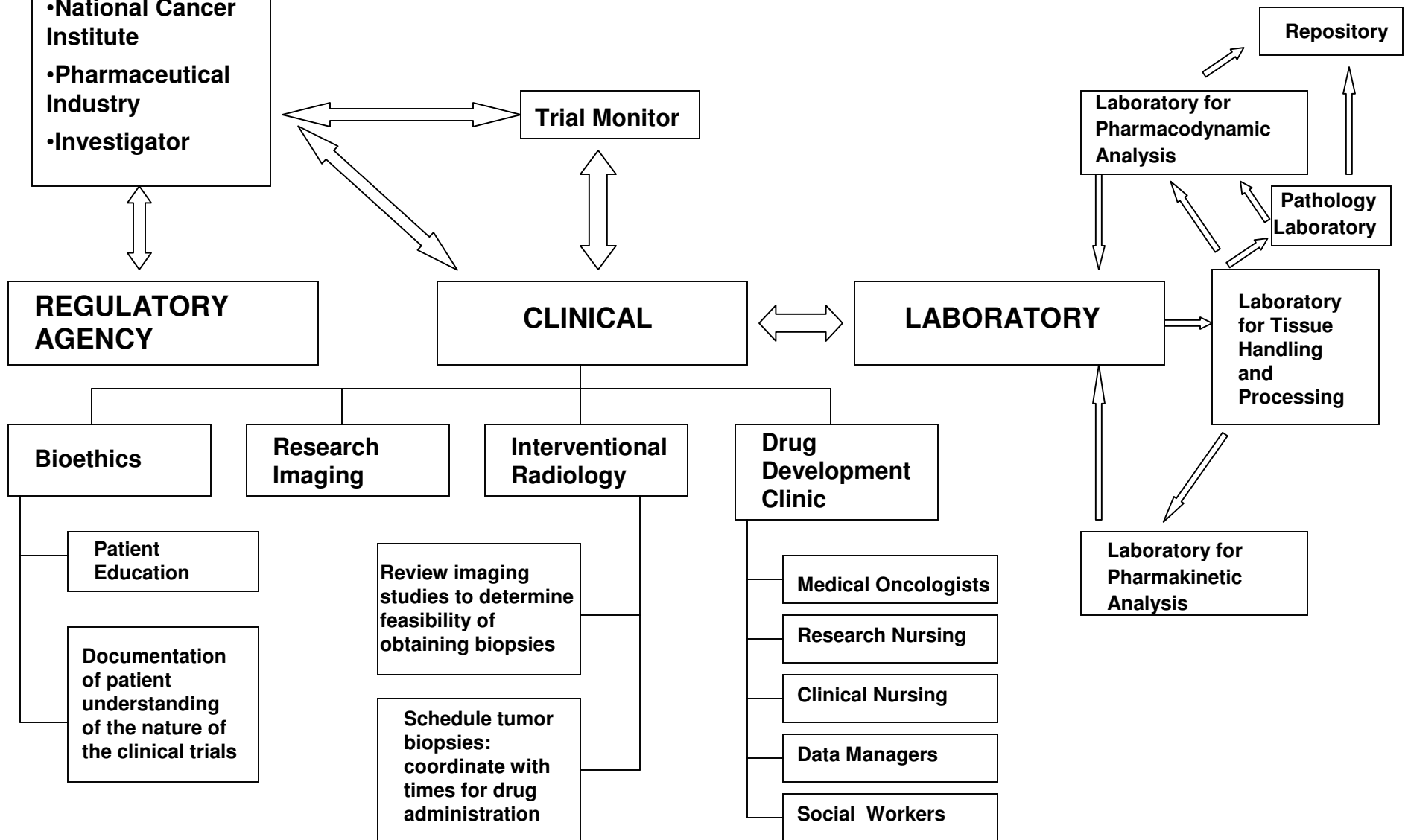
b-Actin



Actin Settings
Min 20.0
Max 3000.0
30 sec exp.

Separated on an 8% Tris-Gly Gel

Integrated Phase 0 Research Team



Phase 0 Statistical Issues

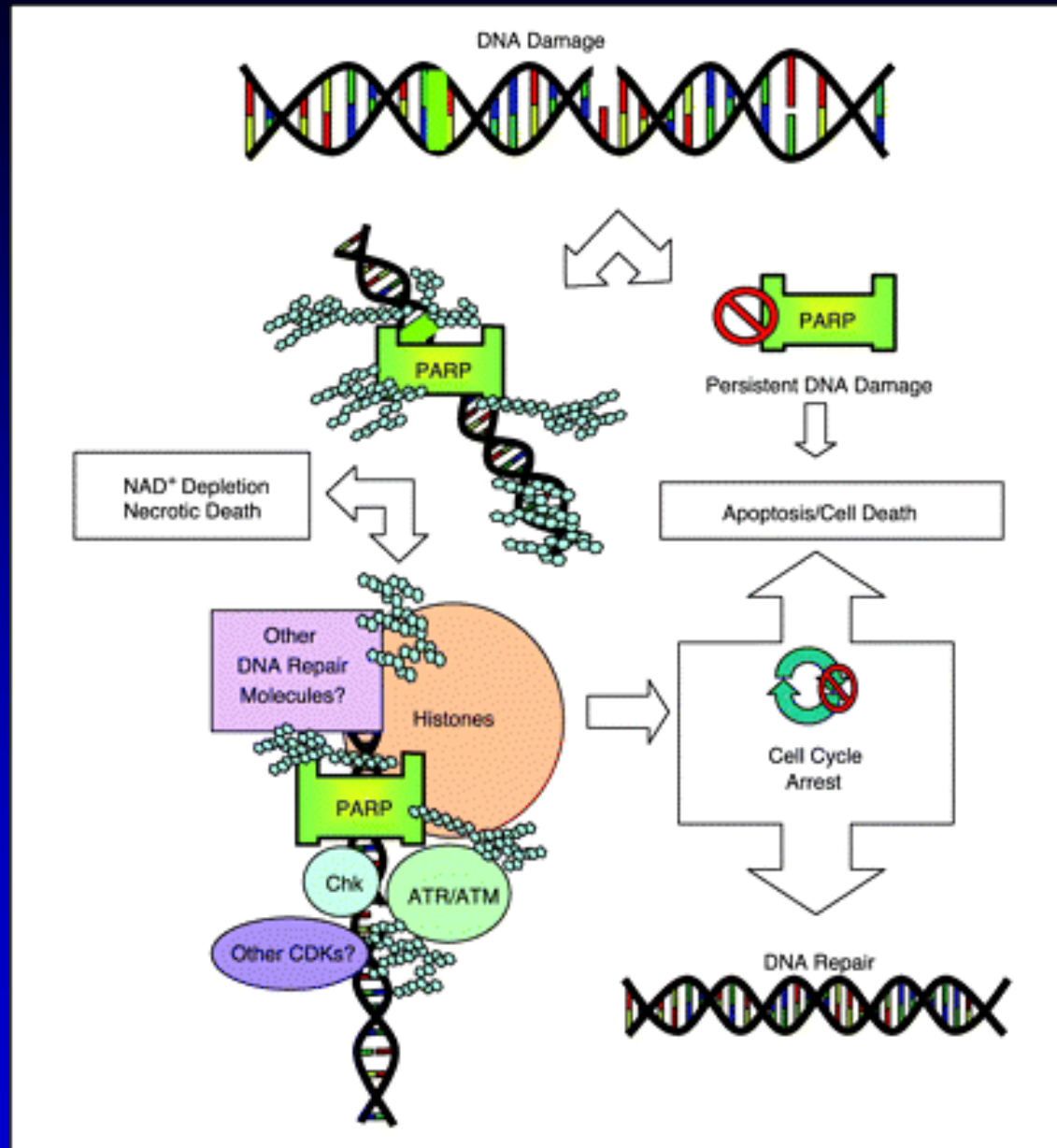
- v Limit sample size to 6-15 patients, generally
- v Define primary endpoint(s) prospectively
- v If possible, obtain a measure of intra-patient variability for the pre-treatment endpoint values
- v Define thresholds (binomial) for declaring treatment effect on biomarker (efficacy) for an individual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

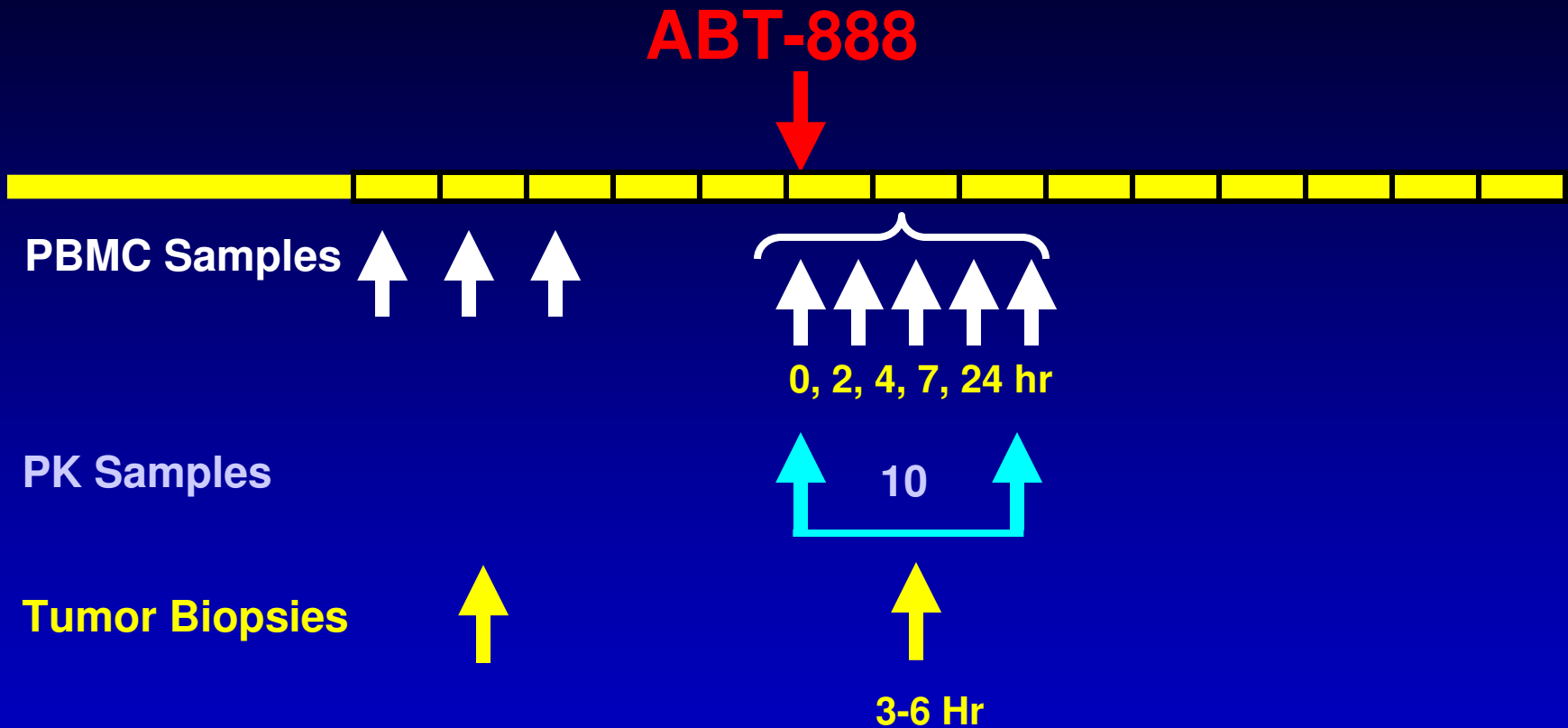
✓ Primary:

- ✓ 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

Study Schema



Tumor biopsies planned:

- Significant PARP inhibition in PBMCs from at least 1 of the 3 participants at a given dose level, OR
- Plasma C_{Max} of 210 nM was achieved in at least 1 participant

Dose Escalation

Dose Level	Dose
Level 1	10 mg
Level 2	25 mg
Level 3	50 mg
Level 4	100 mg
Level 5	150 mg

← Predicted

3 patients at each dose level

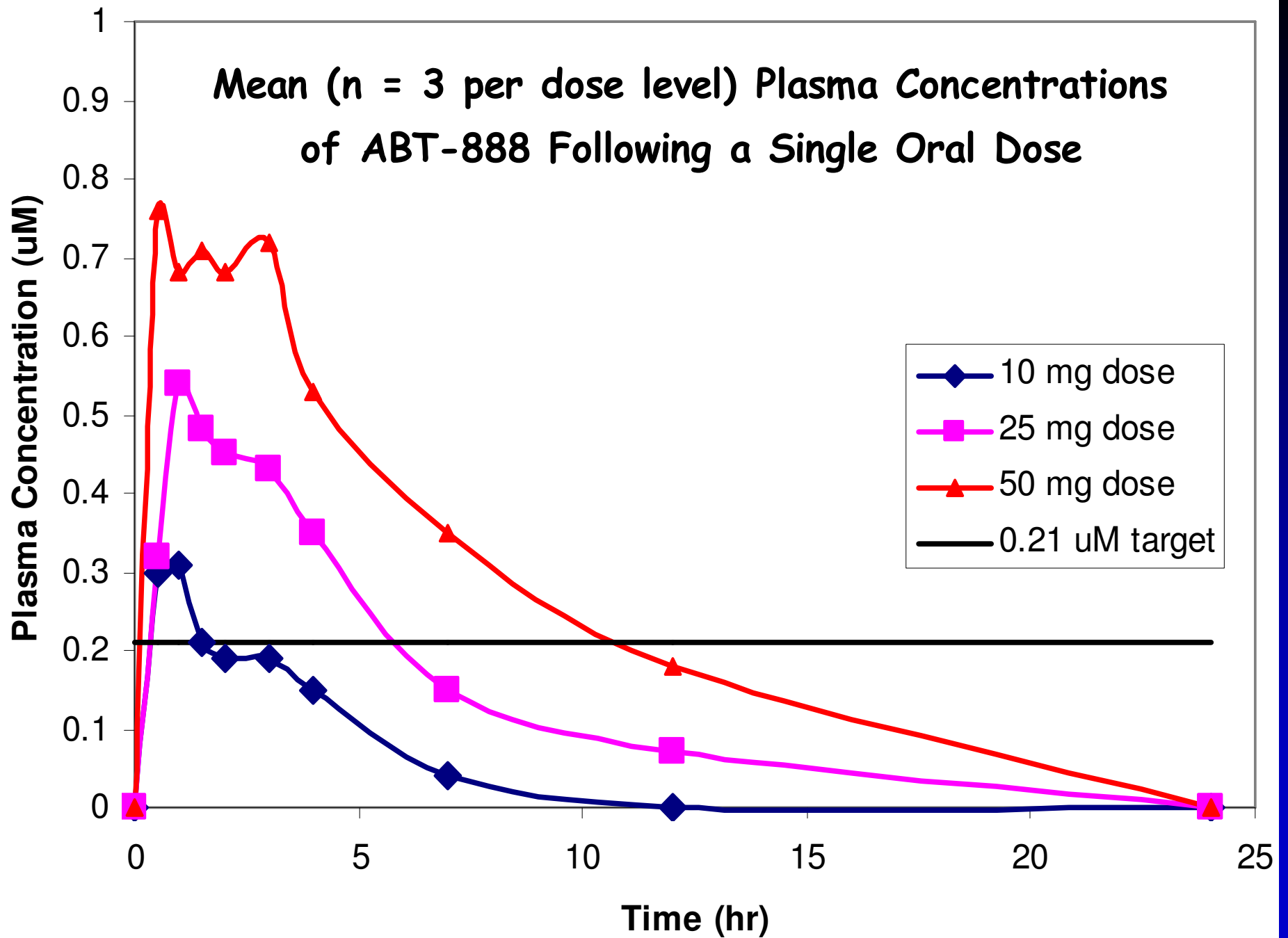
The objective of dose escalation is to investigate a PD endpoint, *i.e.* inhibition of PARP activity and not to determine the MTD

Dose escalation continued with the goal to achieve significant PARP inhibition in tumor samples in 3 out of 3 participants at 2 dose levels

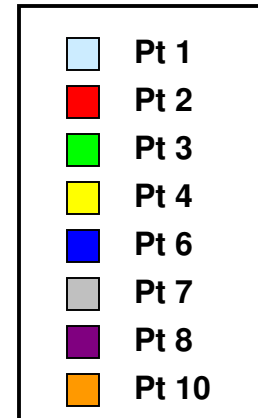
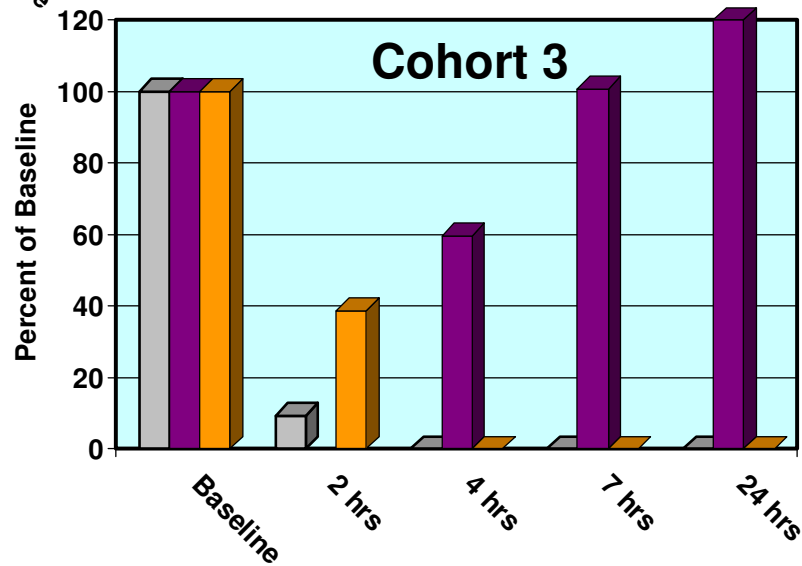
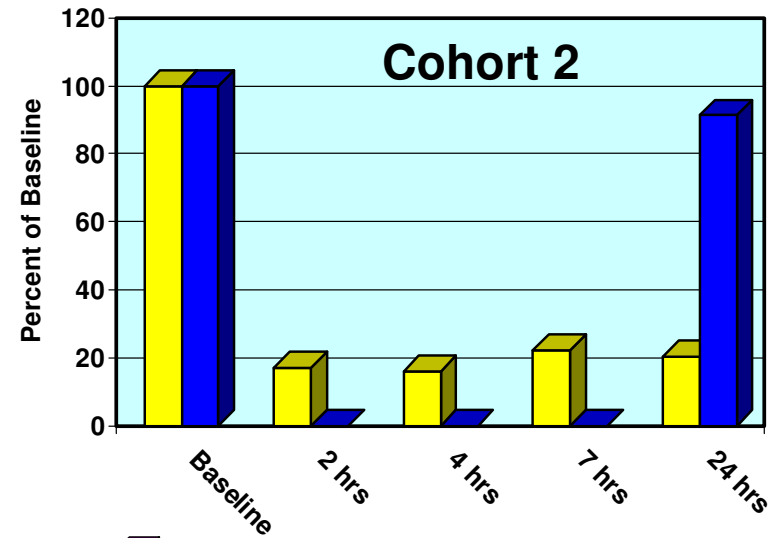
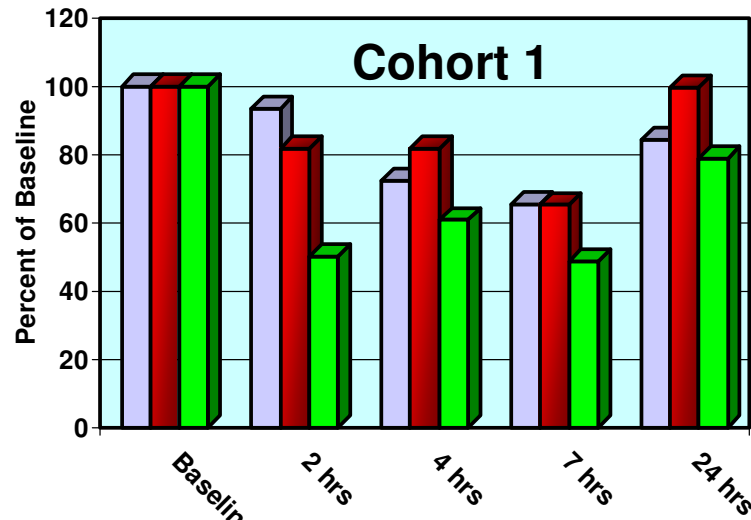
Trial Results (To Date)

- ∨ **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**

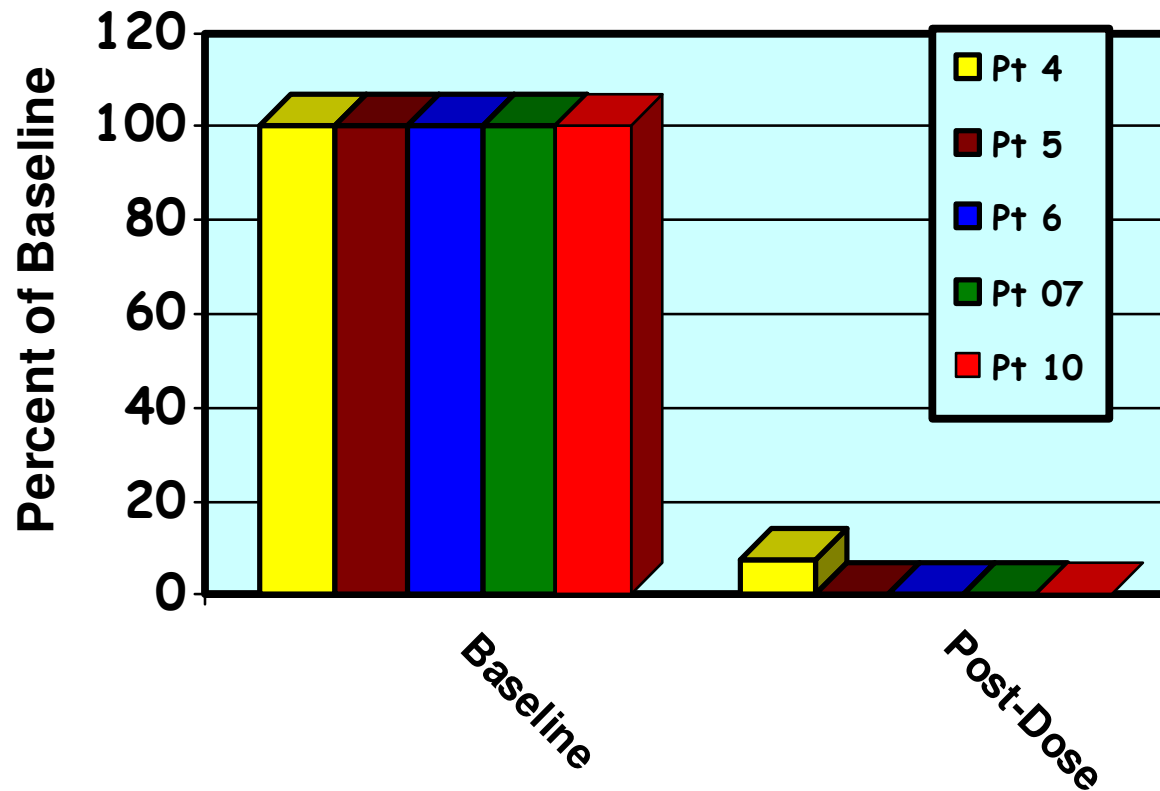
Mean (n = 3 per dose level) Plasma Concentrations
of ABT-888 Following a Single Oral Dose



PAR Inhibition in PBMCs

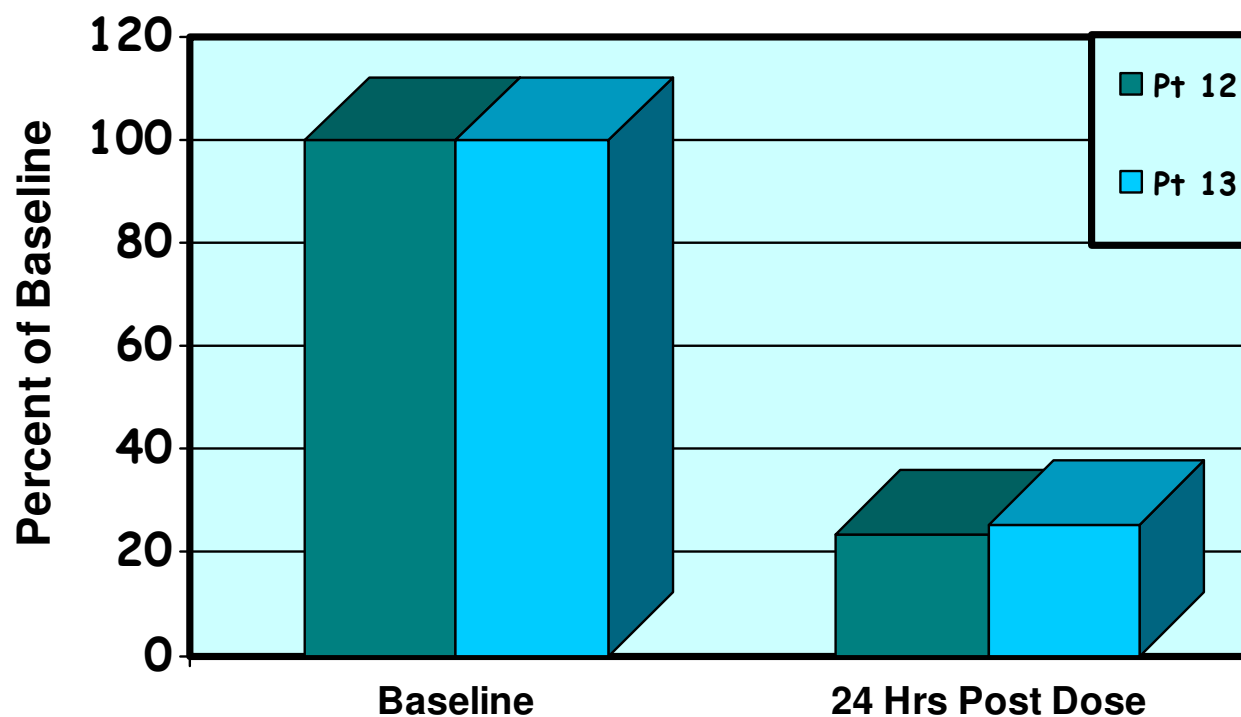


PAR Inhibition in Tumor Biopsies



PAR Inhibition in Tumor Biopsies 24 Hours Post Dose

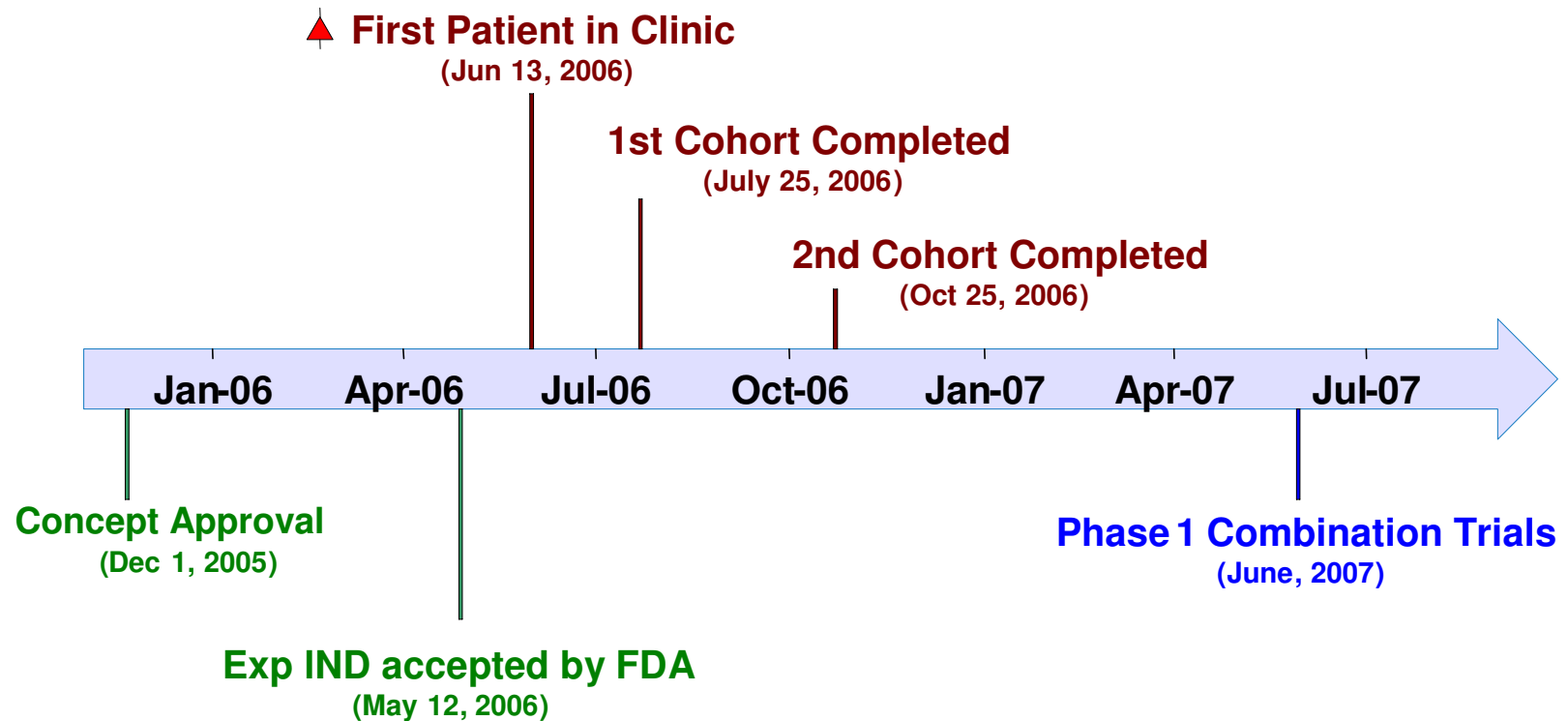
At the 50-mg dose level, 2 additional patients underwent a tumor biopsy at 24 hours post ABT-888 administration to evaluate time to recovery of PARP activity.



First Phase 0 - Where Are We Now?

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

First Phase 0 Trial - Timeline



When Will Phase '0' Trials Be Helpful?

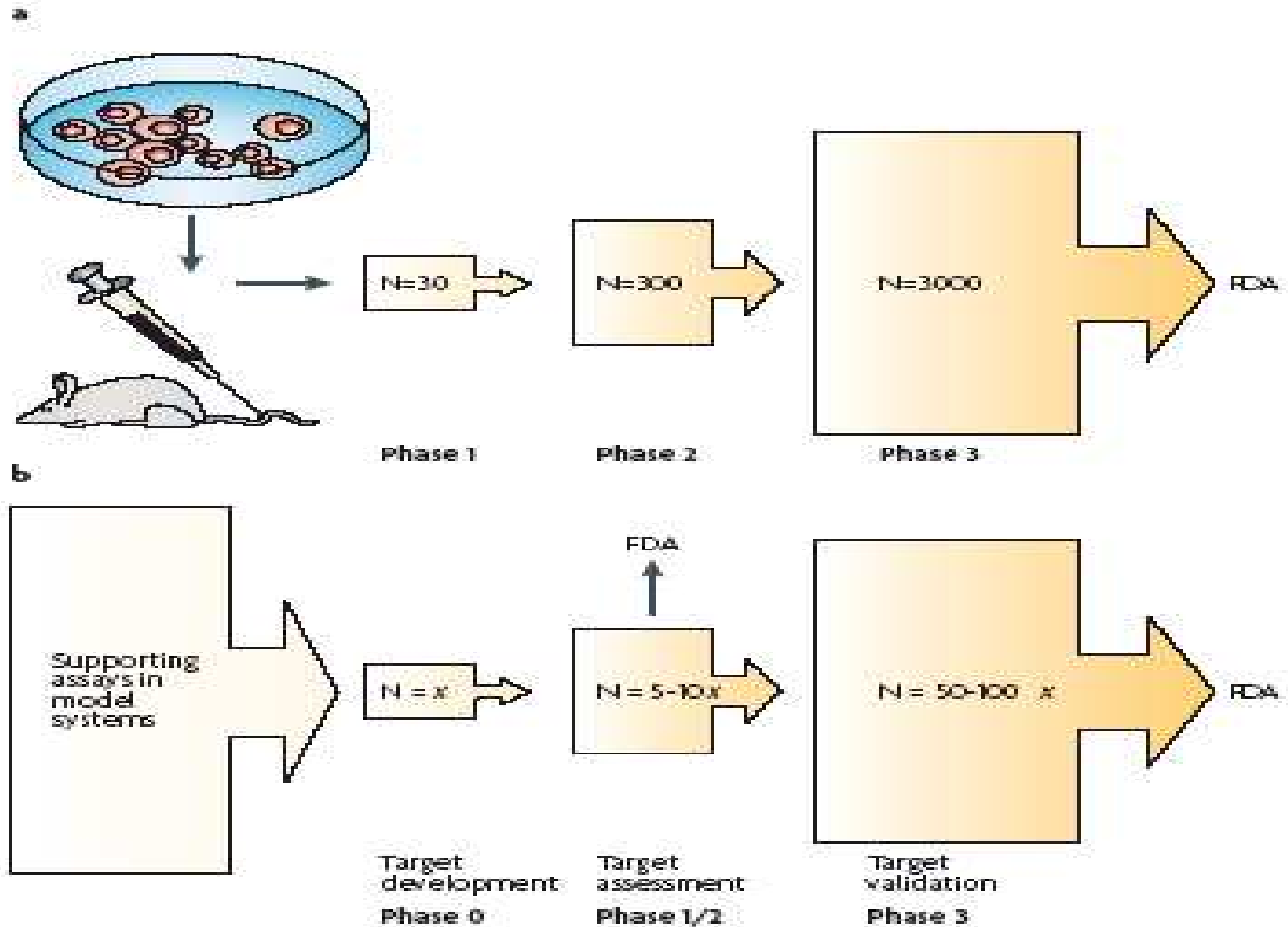
Consider Phase '0'

- ▼ 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

DCTD

- ✓ Joseph E. Tomaszewski
- ✓ Jerry Collins
- ✓ Tony Murgo
- ✓ Jennifer Low
- ✓ Oxana Pickeral
- ✓ Melinda Hollingshead
- ✓ Gurmeet Kaur
- ✓ Sherry Yang
- ✓ Larry Phillips
- ✓ Larry Rubinstein
- ✓ Seth Steinberg
- ✓ Barbara Mroczkowski

FDA

- ✓ Ray Klecker

CCR

- ✓ Shivaani Kummar
- ✓ Martin Gutierrez
- ✓ Robert Wiltrout
- ✓ Lee Helman

NCI Frederick

- ✓ Ralph Parchment
- ✓ Robert Kinders
- ✓ Jay Ji
- ✓ Yiping Zhang
- ✓ Tiziano DiPaolo
- ✓ William Jacob
- ✓ Vali Sevastita
- ✓ Melanie Simpson
- ✓ and numerous technical support staff