

Role of Phase 0 Trials in Anti-Cancer Drug Development

Dr. Shivaani Kummar

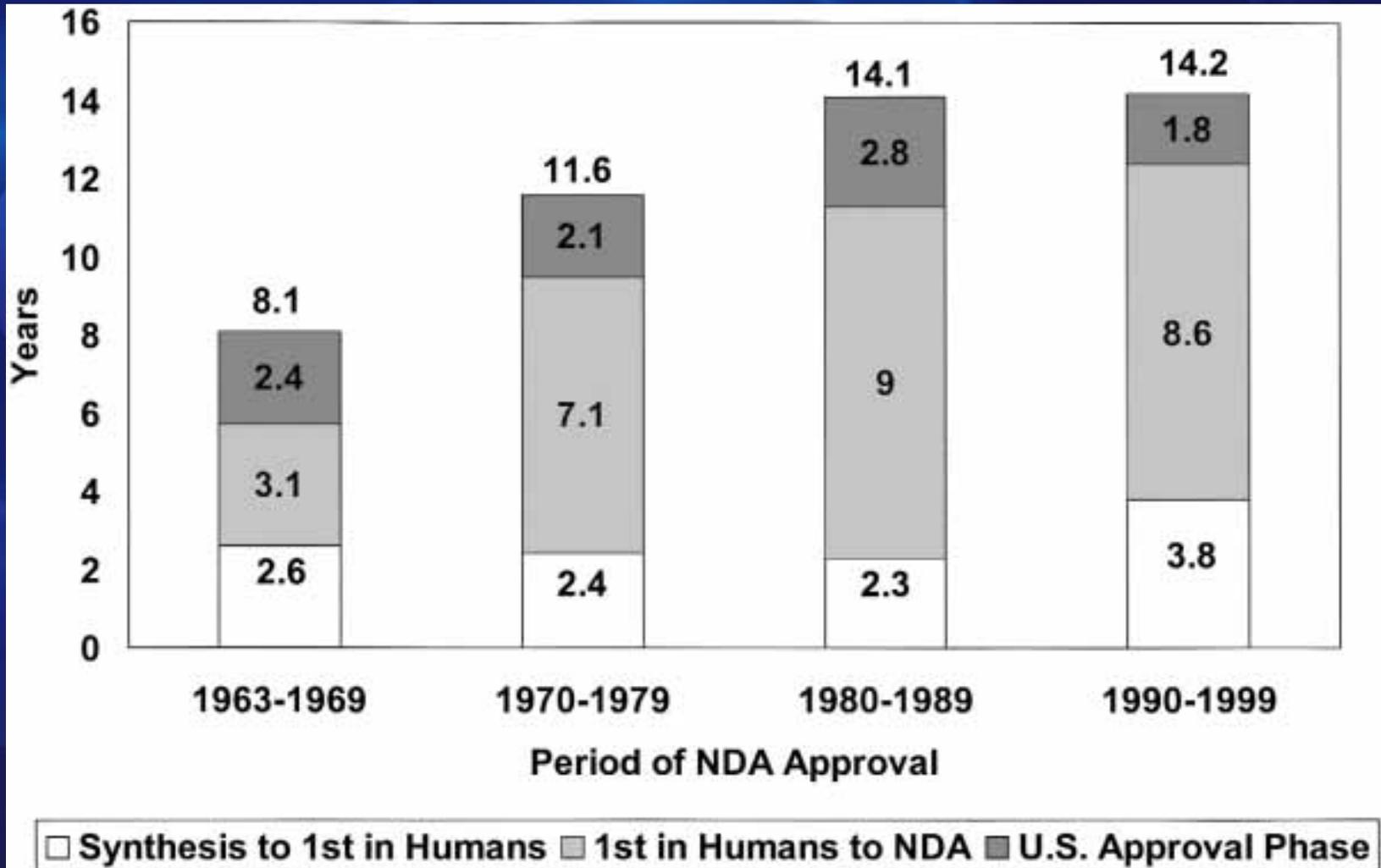
Head, Early Clinical Trials Development
Office of the Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute

September 21, 2011

Outline

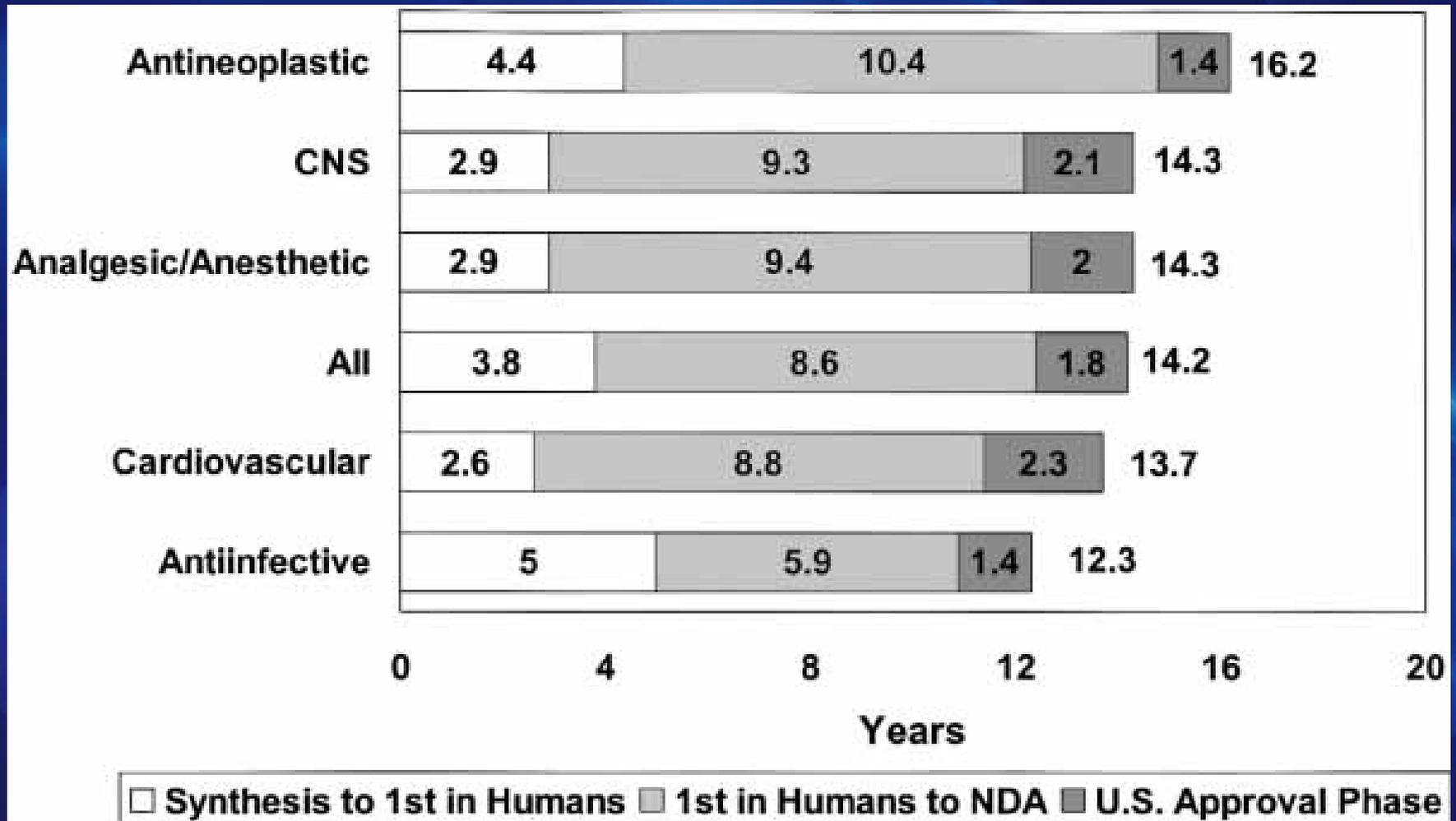
- **Where do we stand in Oncology drug development?**
- **What do we need to develop effective new drugs?**
- **FDA's Exploratory Investigational New Drug application**
- **Concept of Phase 0 trials**
- **How can Phase 0 trials expedite the drug development process?**
- **Developmental Therapeutics Clinic, NCI –Our experience with the first phase 0 trial in oncology**

Total Drug Development Time From Synthesis to Approval



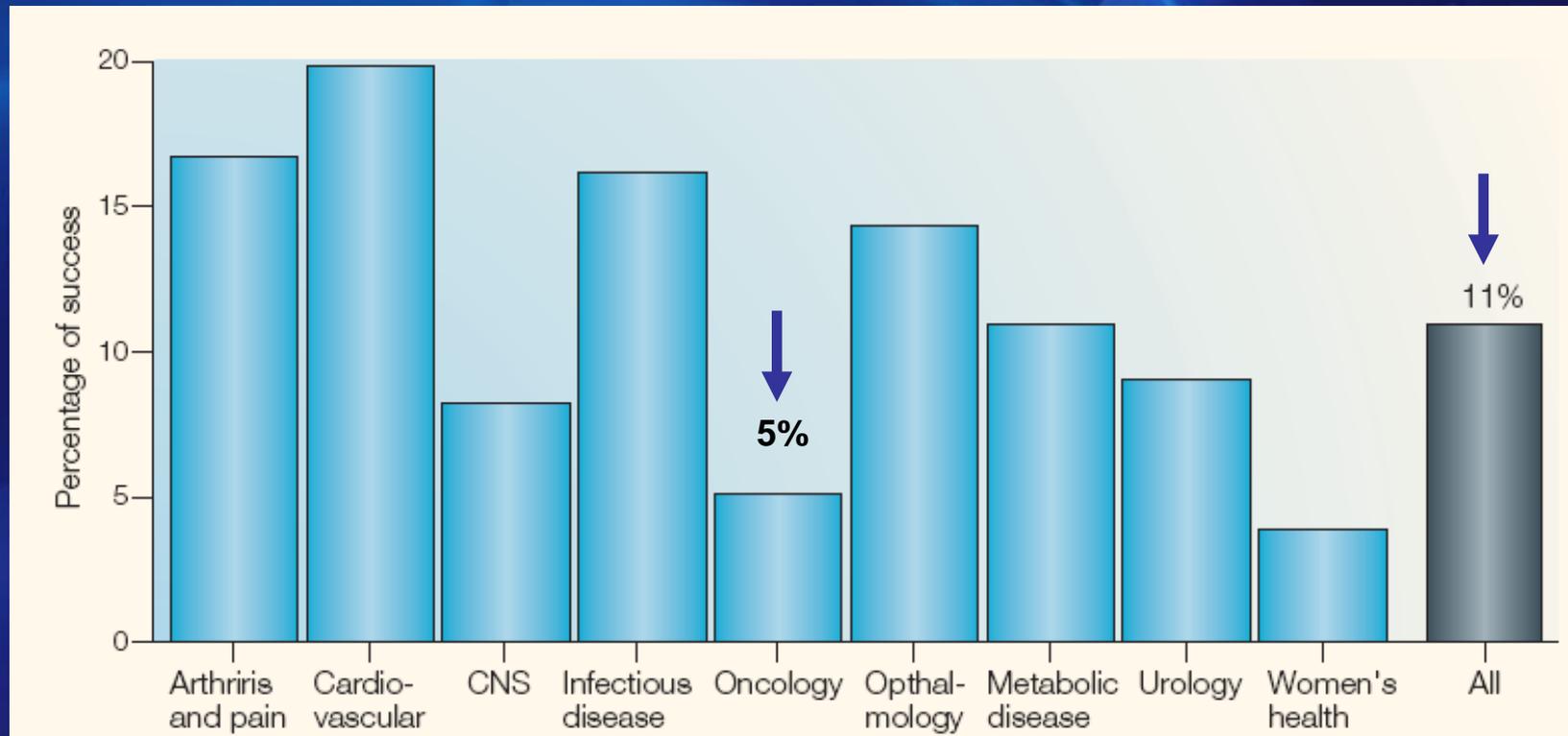
DiMasi JA, et al. *Clin Pharmacol Ther* 2001;69:286-96

Timeline for Drug Development



DiMasi JA, et al. *Clin Pharmacol Ther* 2001;69:286-96

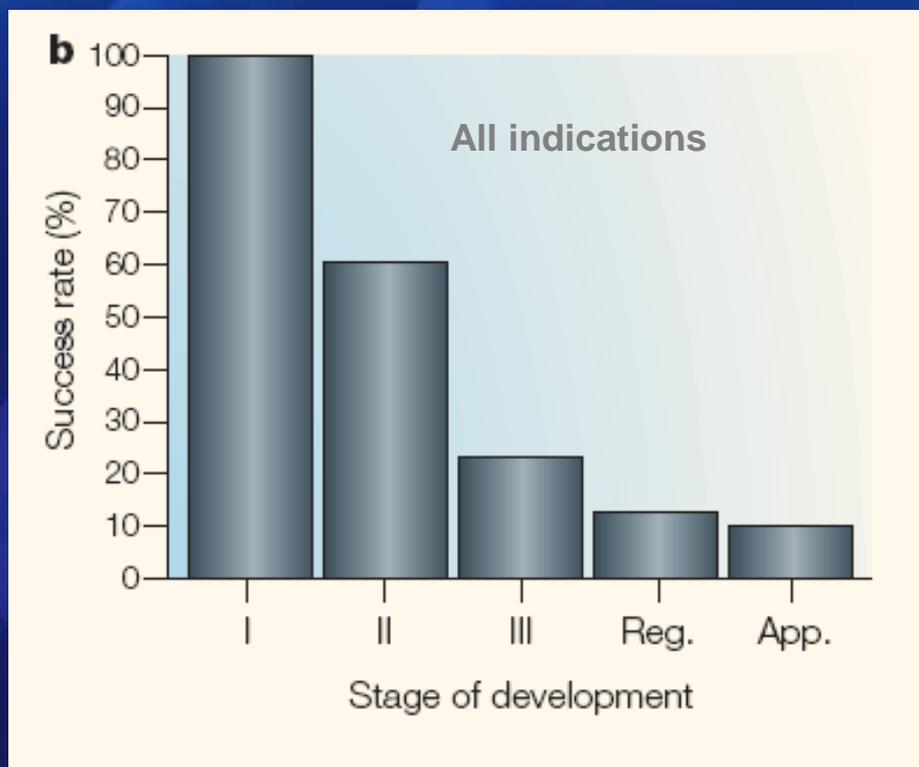
Success Rates from First-in-Human to Registration



Data from 10 biggest drug companies from 1991-2000

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**

Molecularly Targeted Agents

Rethinking The Drug Development Paradigm

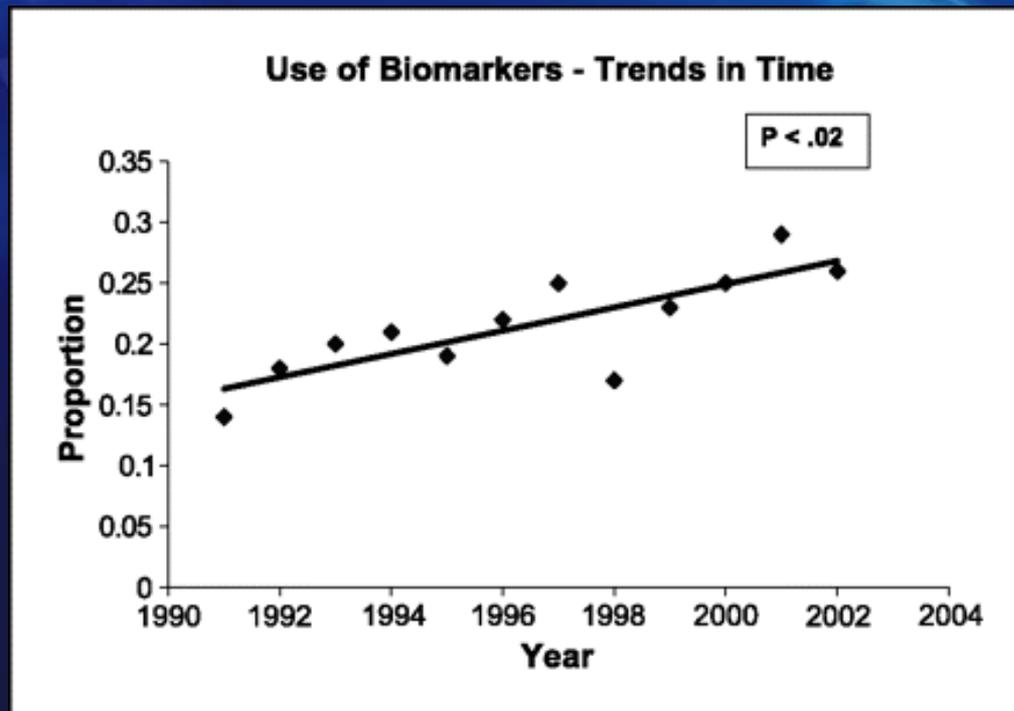
- Does the agent affect the putative target in tumor?
- Is more really better?
 - Should we push doses to levels of tolerance or level of target inhibition?
 - Concept of Optimal target inhibition
 - Develop an understanding of drug effects in tumor cells and normal cells *in vivo*
 - Is drug effect associated with anti-tumor activity?
 - PK- PD relationships, effective exposures
 - What is the required level and duration of effect to produce therapeutic activity

Rethinking the Drug Development Paradigm

- **What do we need?**
 - Ways to measure drug levels
 - Ways to assess changes in target following drug administration
- **When do we need these?**
 - Developed prior to initiation of clinical trials
 - Integration of such assays into early clinical trials

Rethinking the drug development paradigm

- What is happening?



Goulart, et al. *Clin Cancer Res* 2007

FDA's Exploratory IND Guidance

Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies

*Conceived under FDA's "Critical Path" initiative to
help sponsors identify promising candidate drugs
more quickly*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2006
Pharmacology/Toxicology

Phase 0 Trials

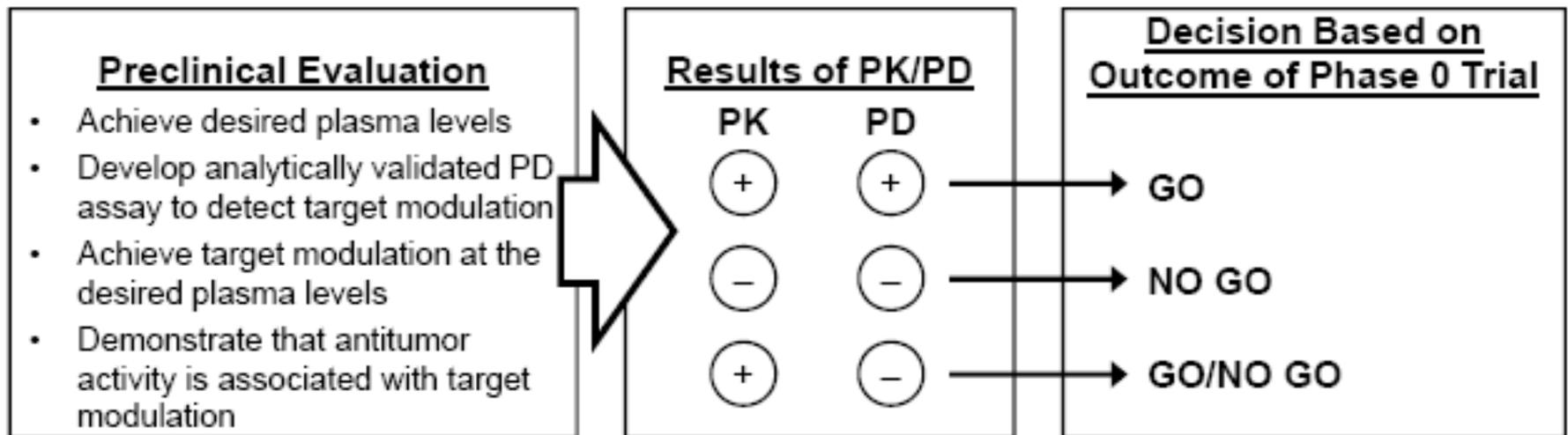
- Early-phase clinical trials conducted under the exploratory IND guidance (pre-Phase I trials)
- Goals are to generate data to:
 - Inform and increase chance of success of the subsequent development of an agent
 - Prioritize compounds so that only promising compounds move to later stages

What Are the Characteristics of a Phase 0 trial?

- First-in-human trials:
 - No therapeutic (or diagnostic) intent
 - Limited number of subjects ($\approx 10-12$)
 - Very limited drug exposure
 - Low, nontoxic doses
 - Limited duration of dosing ($\approx \leq 7$ days)
 - One course
 - Incorporate assessment (using validated assays) of drug levels and effects on target

How Can Phase 0 Trials Improve Efficiency and Success of Subsequent Trials?

- By eliminating an agent very early in clinical development because of poor PD or PK properties
 - Lack of target effect, poor bioavailability, rapid clearance
- By informing subsequent trials



Phase 0 Trials: Logistical and Ethical Considerations

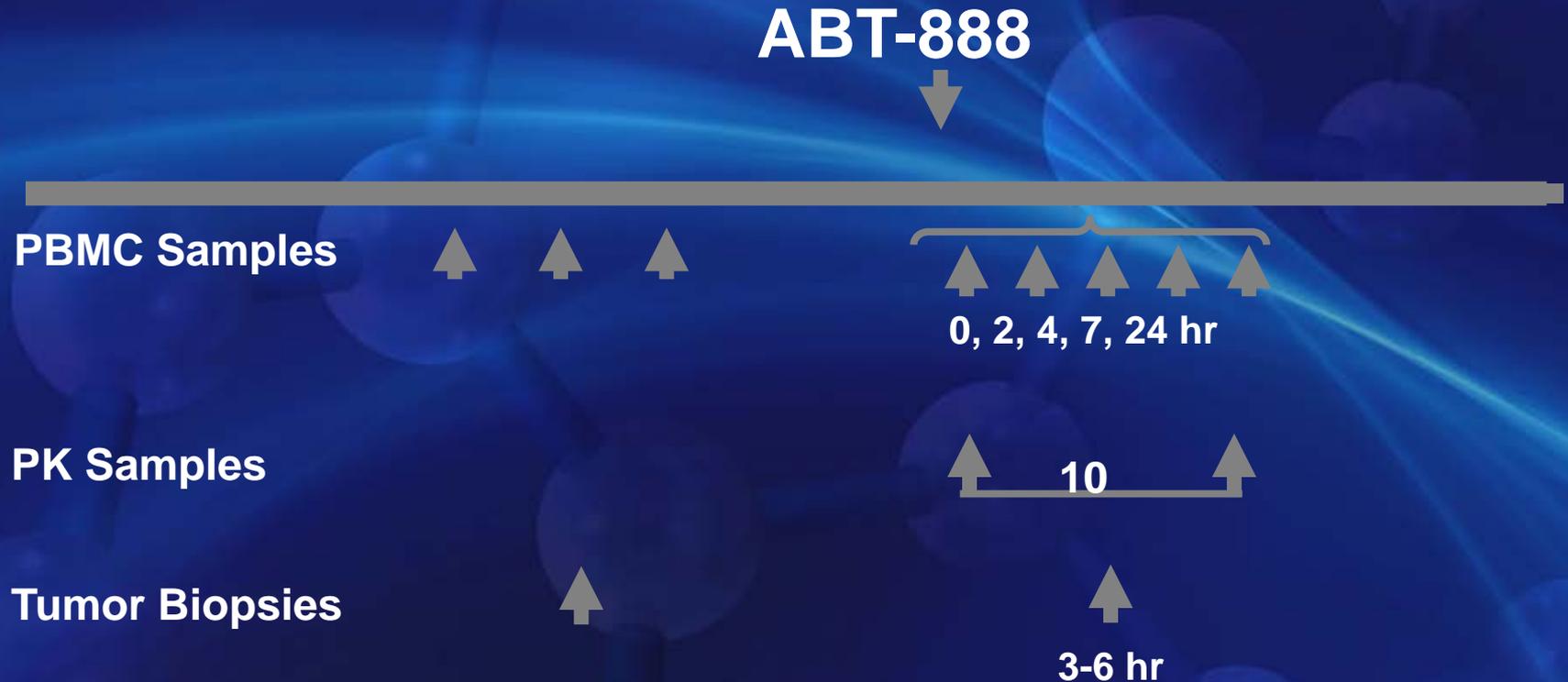
Ethical concerns (they are challenging, but not insurmountable)

- Why would patients agree to participate?
ALTRUISM
- 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
- Institutional Ethics Committee & IRB review and approval
- Informed Consent Process
 - Need to clearly explain the rationale for the study
 - Need to clearly state that there is absolutely no anticipated clinical benefit to the participant

**Phase 0 Pharmacodynamic,
Pharmacokinetic Study Of ABT-888, An
Inhibitor Of Poly (ADP-Ribose)
Polymerase (PARP), In Patients With
Advanced Malignancies**

First PD-driven Phase 0 trial in Oncology

Study Schema



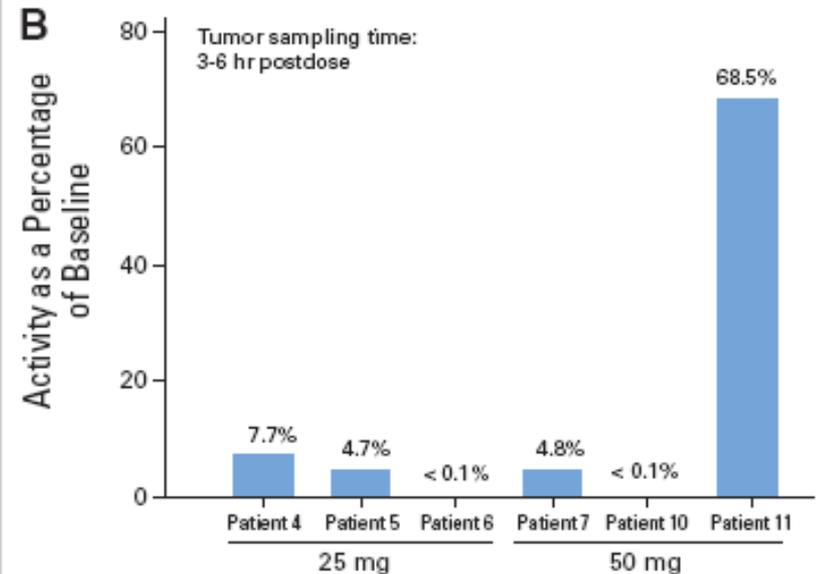
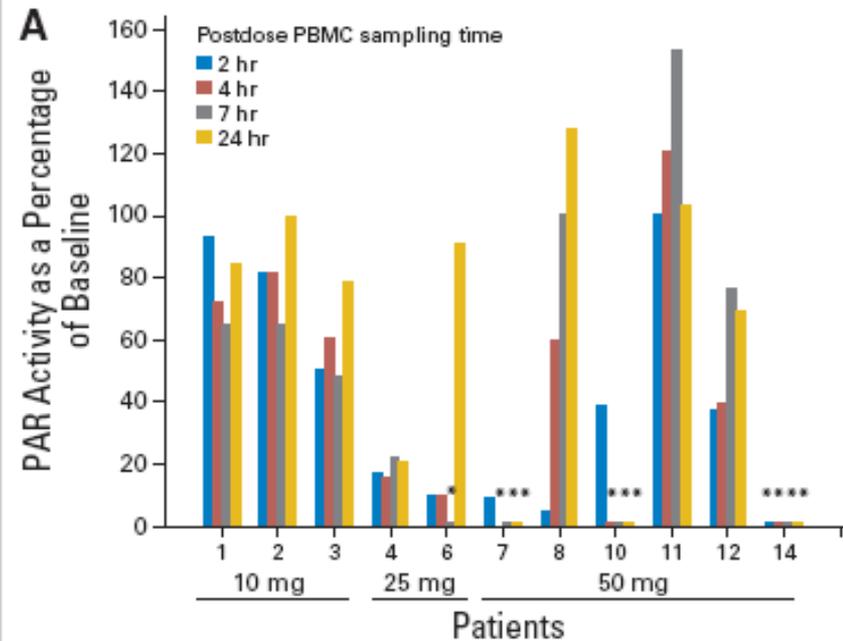
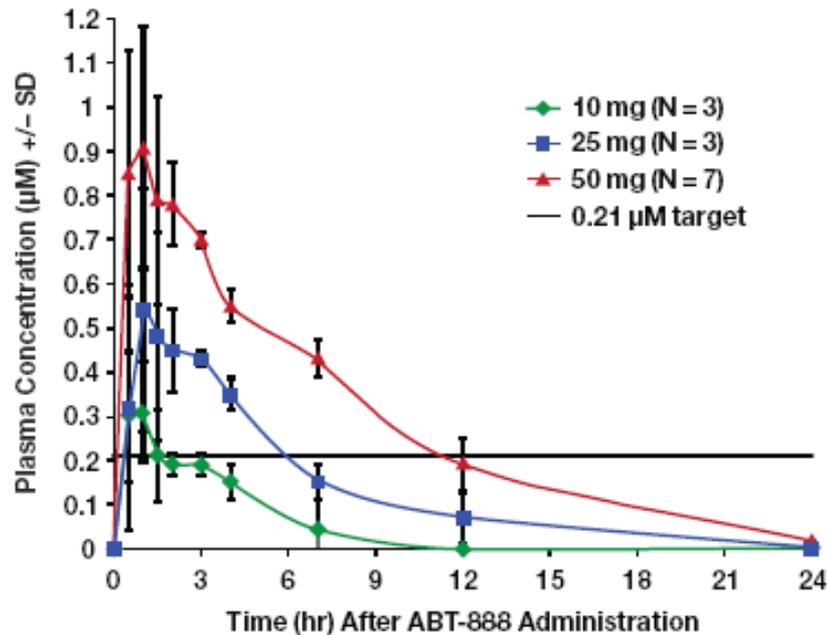
Tumor biopsies planned:

- 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 achieved in at least 1 participant

Phase 0 trial: PK/PD results

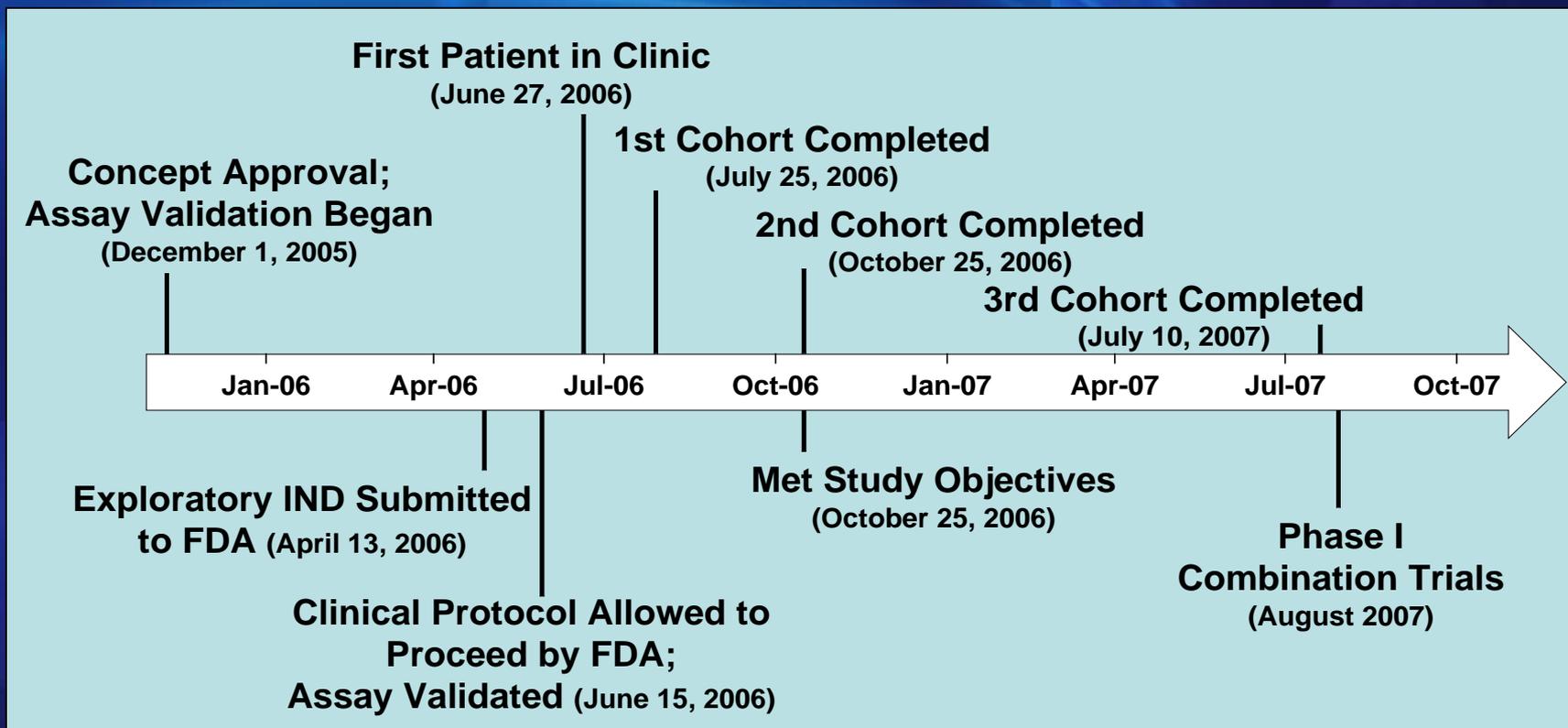


Kummar S, et al. *J Clin Oncol.* 2009;27:2705-11

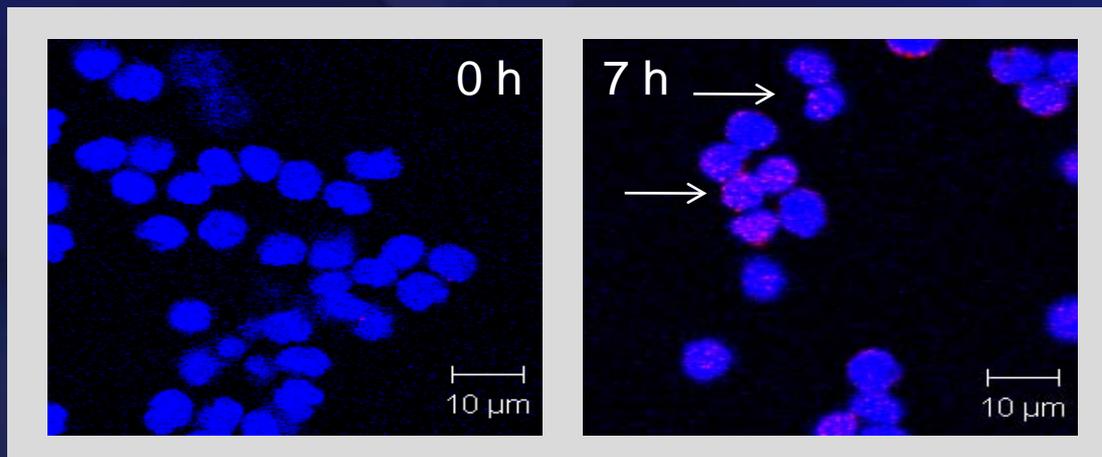
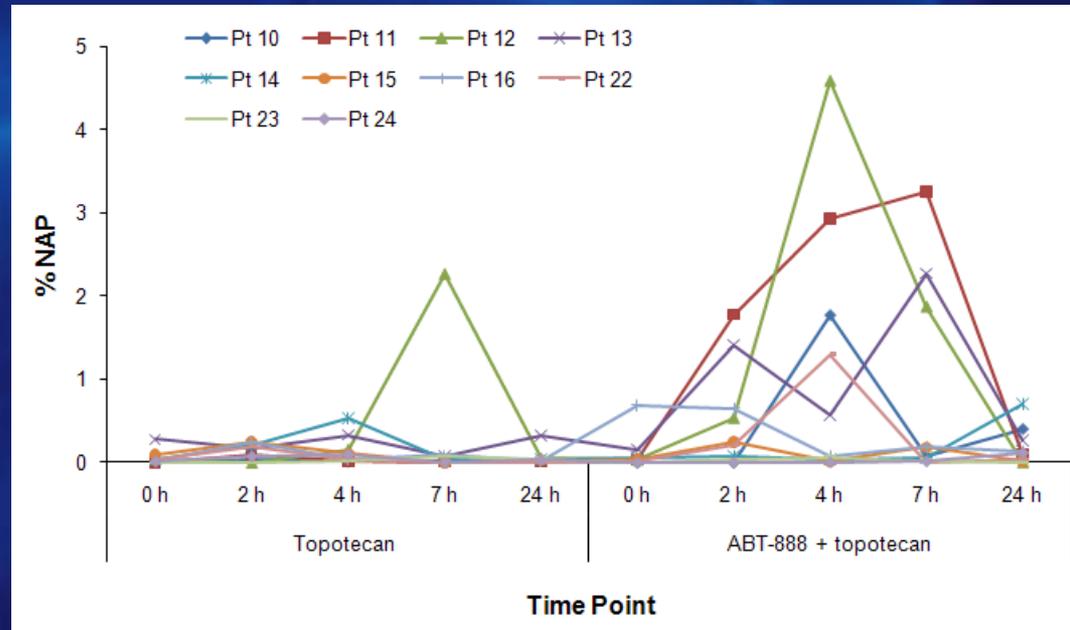
Why Was This Phase 0 Trial Important?

- This pilot first-in-human trial with intensive PK/PD evaluation in a limited number of patients:
 - Determined that ABT-888 inhibits the target in patients at clinically achievable concentrations
 - Provided data that helped design and improve the efficiency of subsequent Phase I/II trials, including combination studies
 - Provided data regarding the relationship between plasma exposure, PARP inhibition in PBMCs and in tumors, raising the possibility of using PBMCs as surrogates in future trials

First Phase 0 – Timelines and What We Achieved

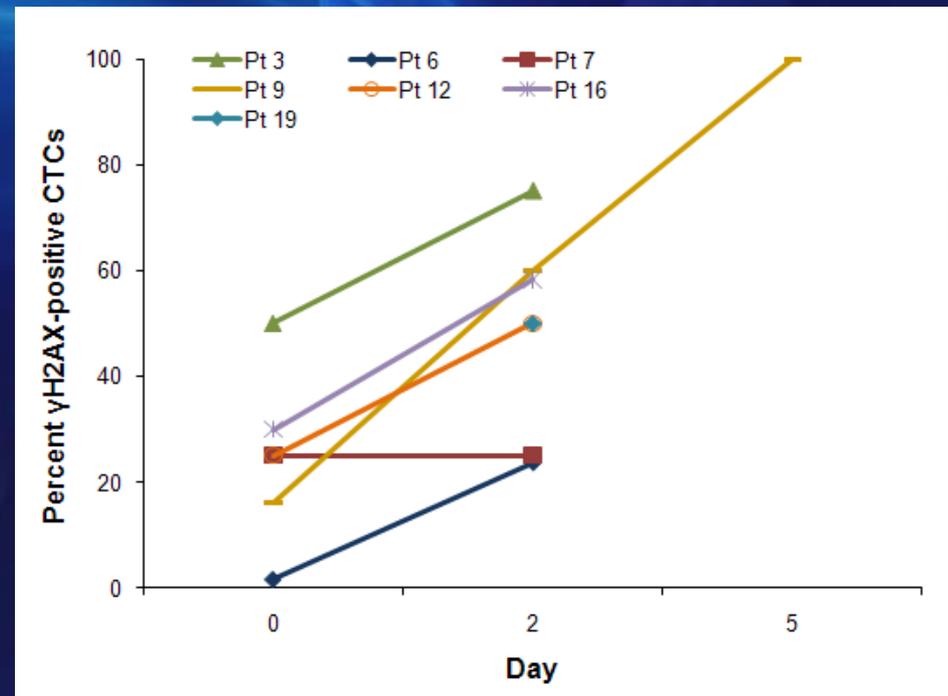
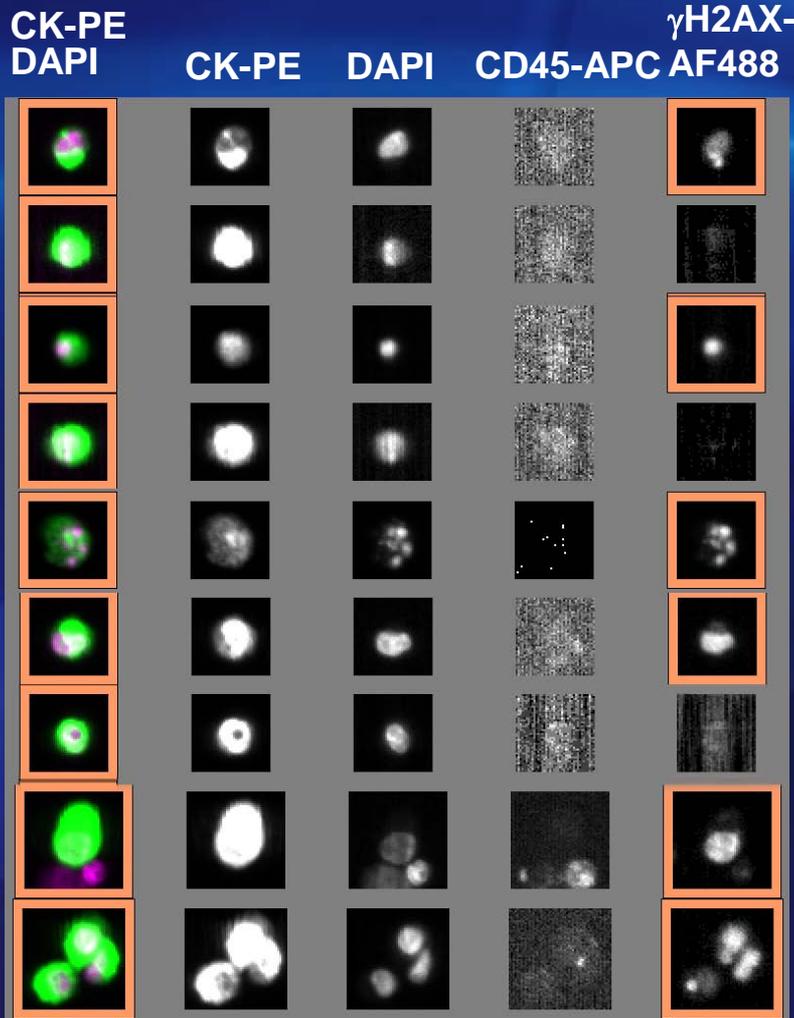


γ H2Ax in PBMCs: Topotecan in Combination With ABT-888

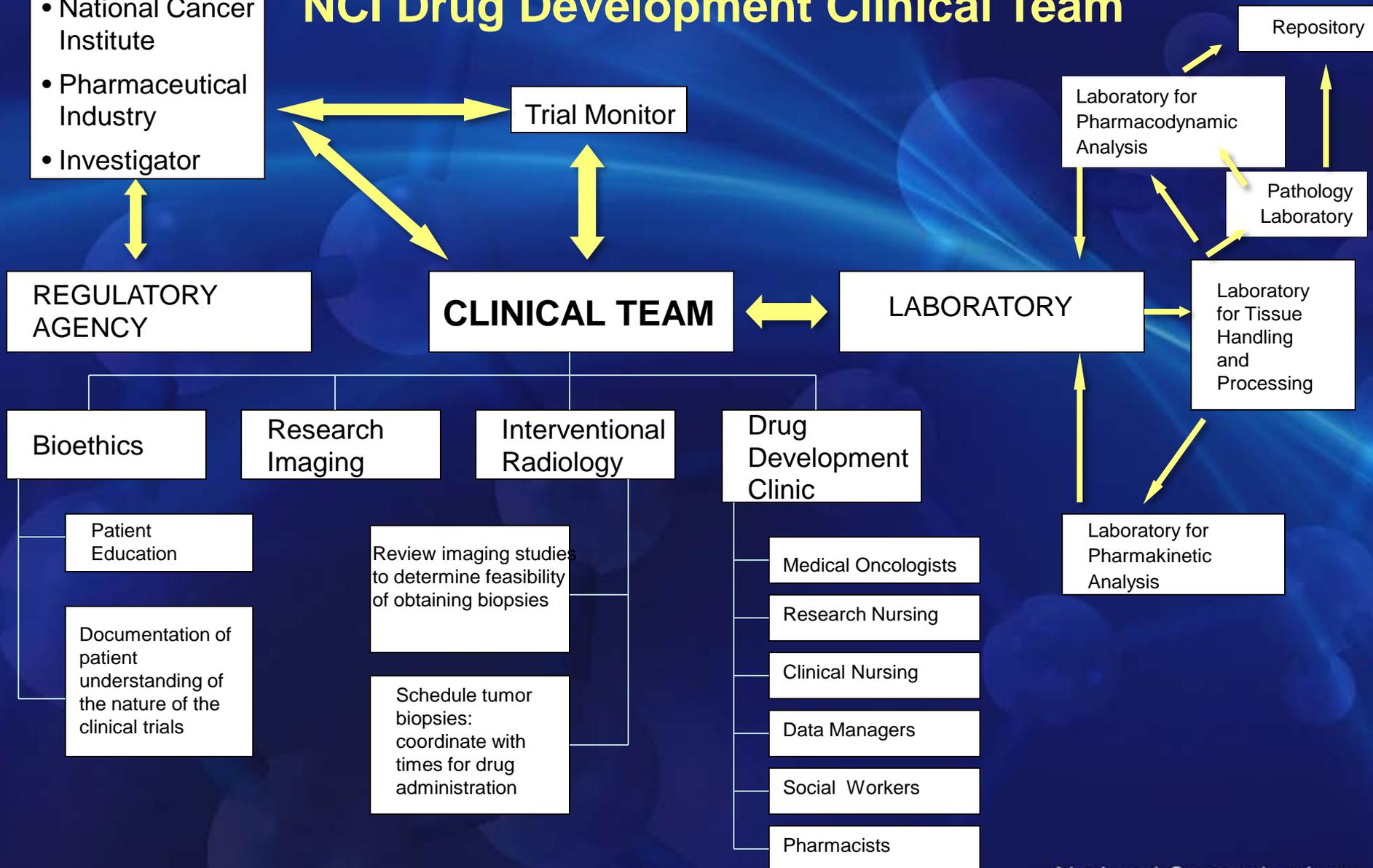


Cancer Res;
71(17); 5626–34,
2011

γ H2AX in CTCs Pre- and Post-Treatment With ABT-888 and Topotecan



Integrated Clinical Research Team: Our NCI Drug Development Clinical Team



Standard Operating Procedures and Training for Validated PD Assays Available Through NCI/DCTD

- **Poly (ADP Ribose) immunoassay for the detection of PAR in needle tumor biopsies and PBMCs**
 - Specimen Collection
 - Sample Preparation
 - Assay SOP and Analysis
- **γ -H2Ax immunofluorescence assay for the detection of histone H2AX phosphorylated at SER139 in circulating tumor cells using the CellSearch® System**
 - Antibody QC and Laboratory Proficiency Testing
 - Assay SOP
- **Coming soon:**
 - Total MET immunoassay in tumor tissue
 - Topoisomerase 1 immunoassay in tumor tissue and PBMCs

Acknowledgements

**All the present and future participants of
clinical trials**

- Developmental Therapeutics Clinical team, NCI
- NCI's Drug Development Team

Types of Phase 0 Trials

Type of study	Objectives	Dose
Pharmacokinetics or imaging	Evaluate biodistribution and target binding	1/100th of the pharmacologically active dose (up to a maximum of 100 µg or 30 nmol for protein products)
Pharmacologic endpoint	Compare pharmacokinetics (bioavailability) of analogs to select lead agent	1/50th of the NOAEL determined in 2-week rodent toxicology studies
Pharmacodynamic endpoint	Measure modulation of target	Less than 1/4 of the rat NOAEL, or dose at which the total exposure measured in human blood samples is 1/2 of that determined in the most sensitive species whichever is lower

Current Challenges in Oncology Drug Development	Phase '0' Trials
Suboptimal use of target assessment and imaging techniques in early phase clinical trials	<p>Biomarker development and assay qualification in human tissues prior to initiation of trial</p> <p>Integration of such assays and/or imaging studies in these trials to establish the mechanism of action <i>in vivo</i> in actual patient samples.</p>
Establishment of MTD as a primary end-point in trials with molecularly targeted agents	Evaluation of target modulation is a primary end-point
Late stage failures with low rates of oncology drug approvals	Allow for the systematic de-prioritization of investigational agents that do not demonstrate expected biologic effects
Long timelines for development of promising agents	Early initiation of first-in-human, proof-of-concept trials that provide data to better inform and expedite subsequent clinical development will shorten drug development timelines
Increasing number of complex trials that require substantial resources	Investing resources in early phase trials involving small number of patients will help prioritize resource allocation for subsequent larger trials