# Phase 1 studies, concepts, practicalities and pitfalls

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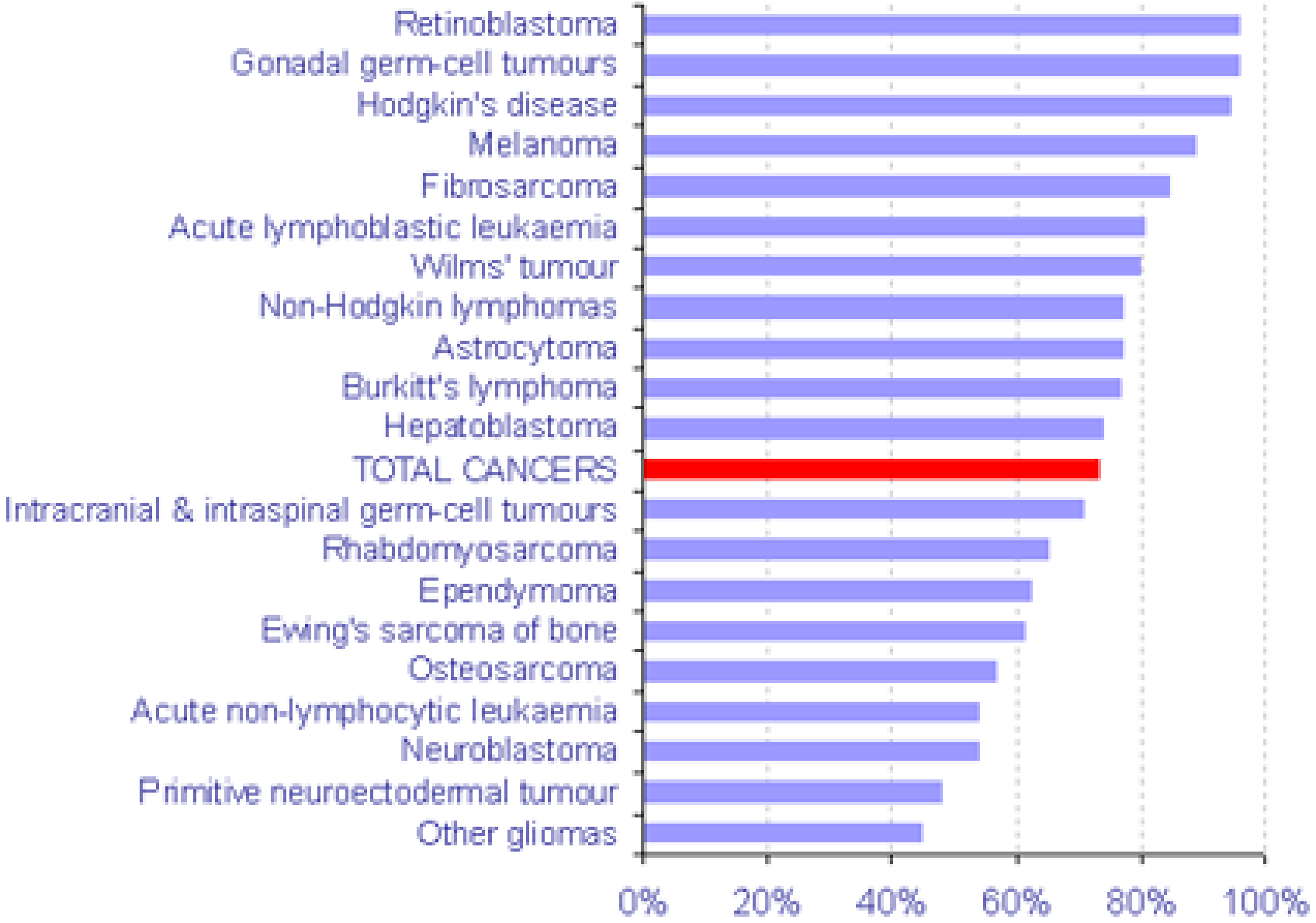
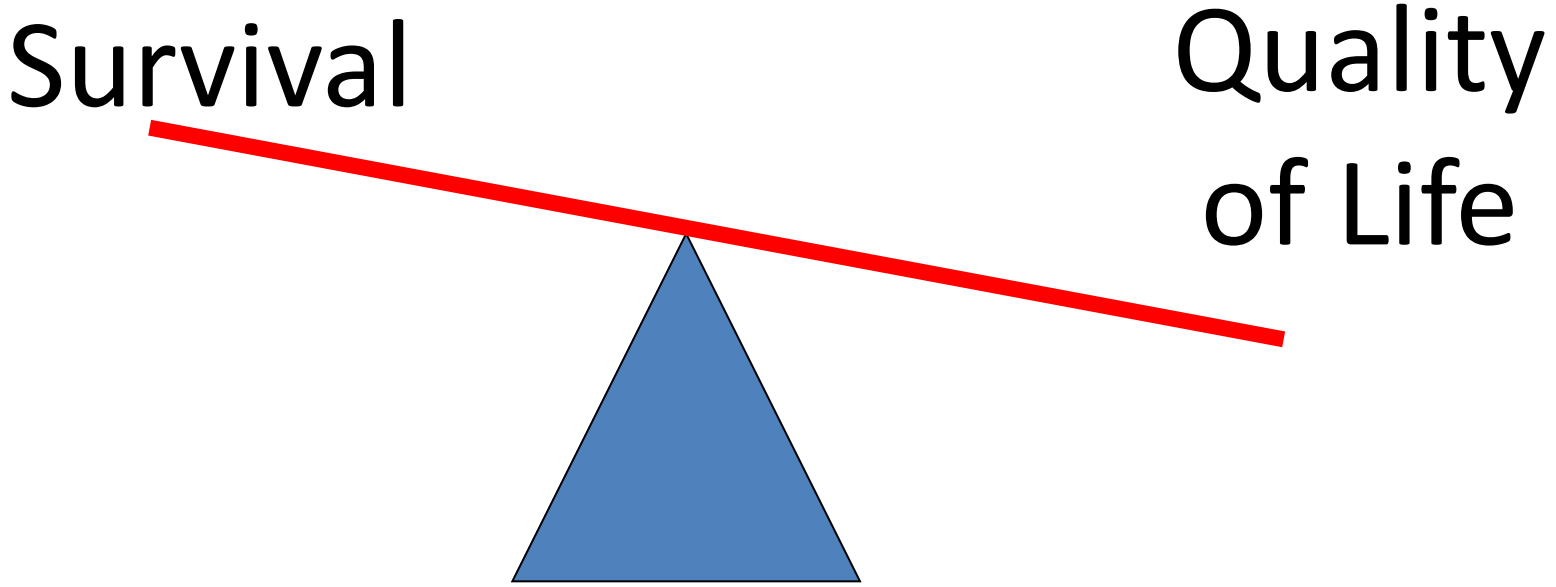
# INTRODUCTION

A clinical trial is defined as an experiment on human being carried out in order to evaluate one or more potentially beneficial therapies.

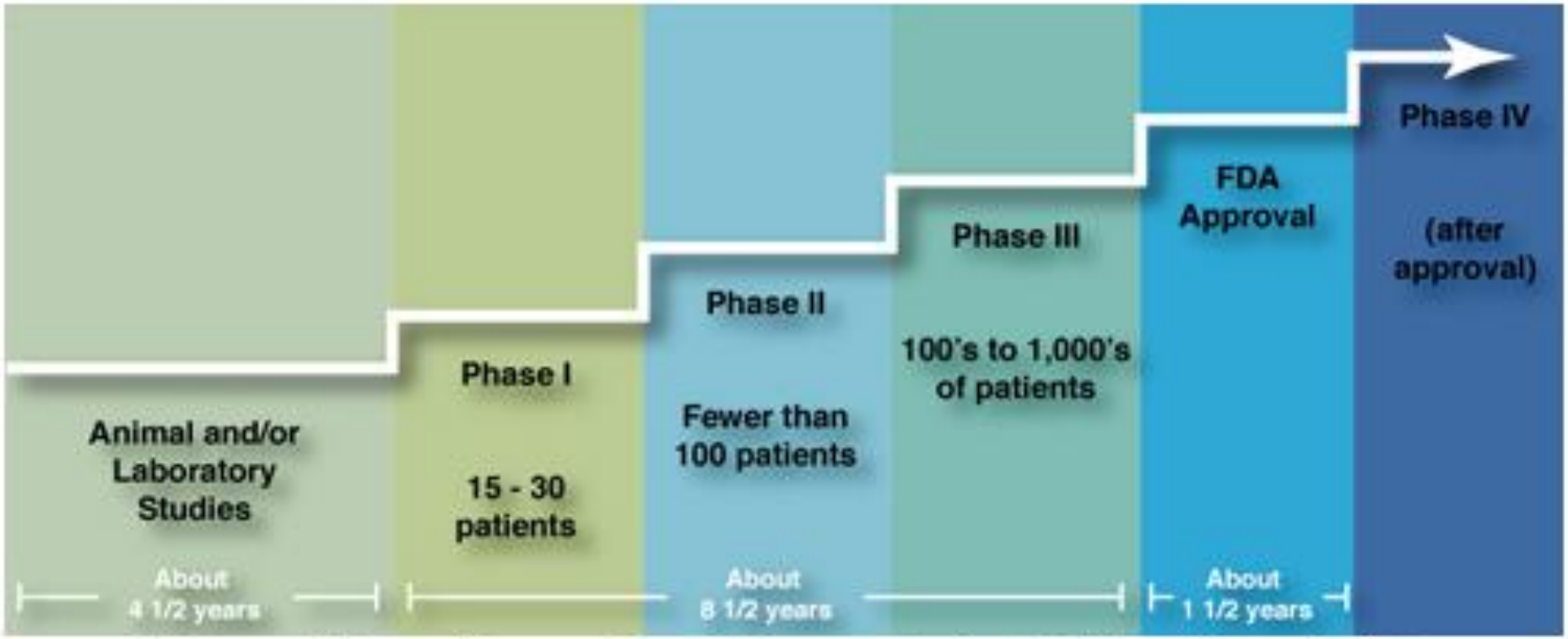
# Why do we need new therapies?



# Why do we need new therapies?



# Drug Development Process




The Drug and Approval Process in the 1990s as reported by the National Cancer Institute.

# Development of New Agents in Oncology

| | Phase I | Phase II | Phase III |
|---|---|---|---|
| Primary objective | MTD | Anti-tumor activity | Efficacy |
| Judgment criteria | Toxicity | Tumor response | Survival |
| Methodology | Dose escalation | "One- or Two-stage" | Randomization |
| N patients | 10-30 | 14-50 | 100s - 1000s |
| PK | Obligatory | Recommended | No |

# PHASE I TRIALS

The principal scientific goal of the Phase I trial of a new agent is to determine a dose suitable for later activity and efficacy testing. **Recommended Phase 2 dose (RP2D).**

We should always remember that cancer patients agree to participate in Phase I trials because of the possibility of therapeutic benefit, even if they realize that the probability of benefit is small.

# Phase I in Adult Oncology
## *"First in Human"*

Pre-requisite:

- Efficacy in experimental models *in vitro* and *in vivo*
- Animal toxicology
- Mutagenesis

# Phase I in Adult Oncology
## *"First in Human"*

Objectives:

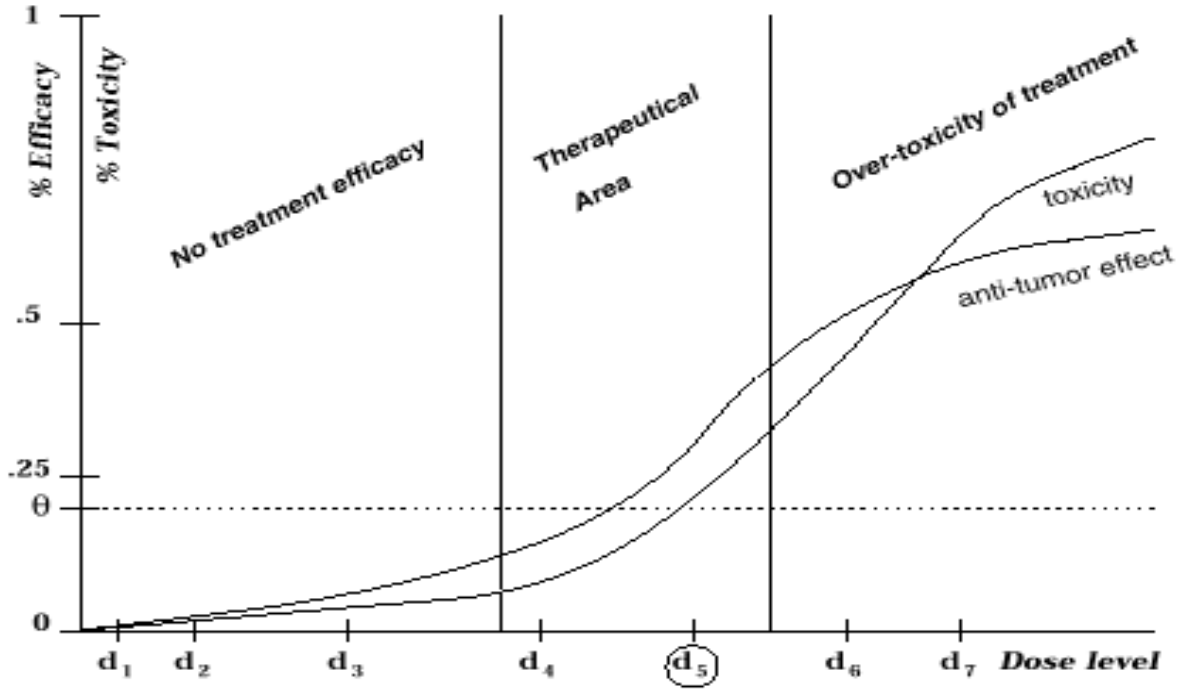
- To determine the maximum tolerated dose (MTD)
- To define the best schedule of administration
- To determine pharmacokinetic parameters, pharmacodynamics

# Phase I in Adult Oncology
## *"First in Human"*

- Patients with refractory or relapsed malignant disease
- First dose level = 1/10 of the lethal dose in mice
- Dose escalation per dose levels according to Fibonacci schemes or CRM
- No healthy volunteers
- *Multiple phase I trials with different schedules of administration*

# Dose Toxicity Relation

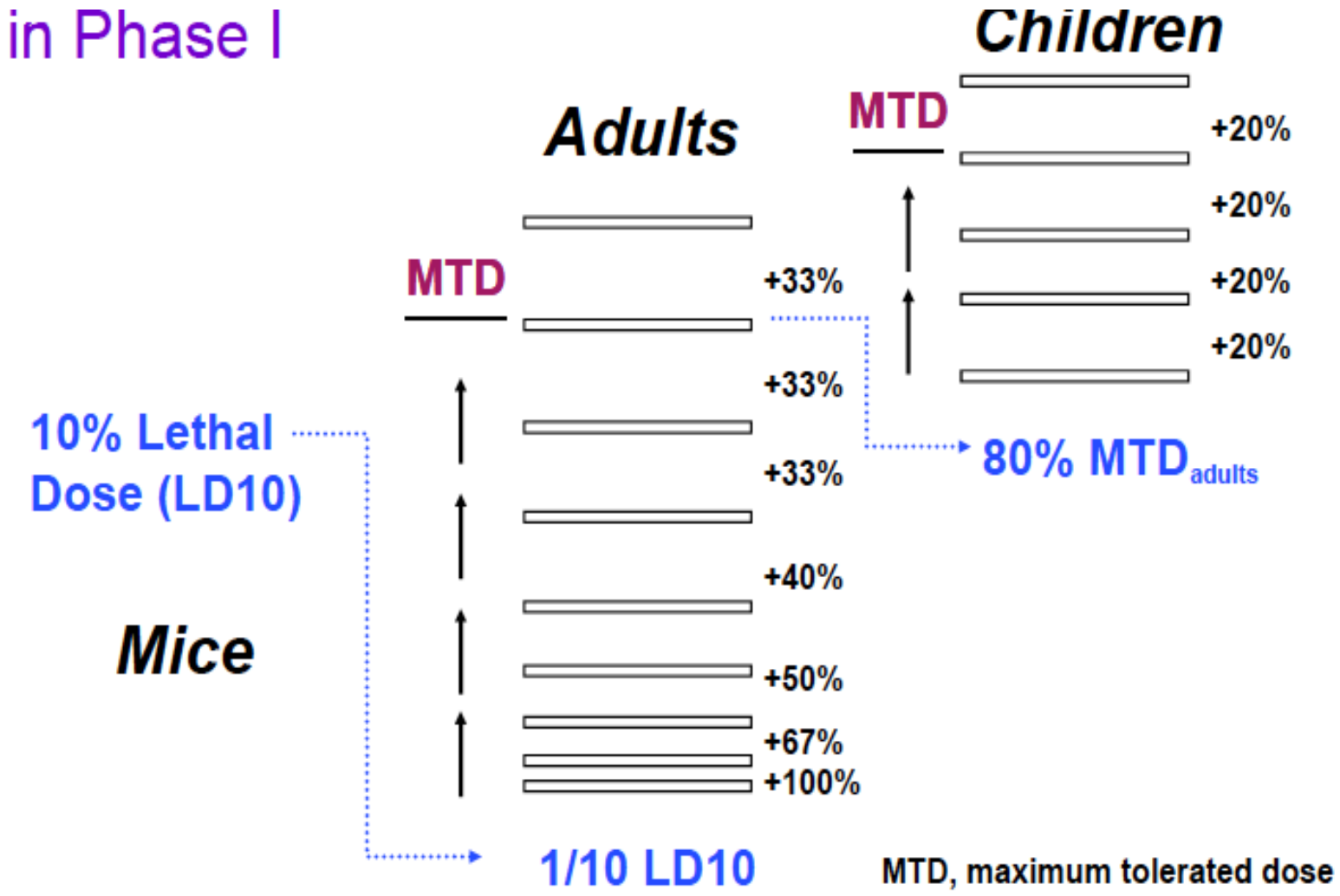
- Assumption: the greater the dose, the more active, but the more toxic.



# ’First in Child’ Phase I Studies

- We would almost never have no adult priori information i.e. First in human is first in child!
- We can therefore use this data to design our trials to be more efficient and ethical!

# Which starting dose?



# Aims, objectives & end-points of Phase I trials

- **Primary objectives**
  - Recommended Phase II dose
    - Maximum tolerated dose (MTD)
    - Optimum Biological Dose (OBD)
- **Secondary objectives**
  - To define the toxicity profile & tolerability
  - To investigate the pharmacokinetics (PK)
  - To investigate the pharmacodynamics (PD)
    - "proof of mechanism study"
  - Preliminary efficacy data

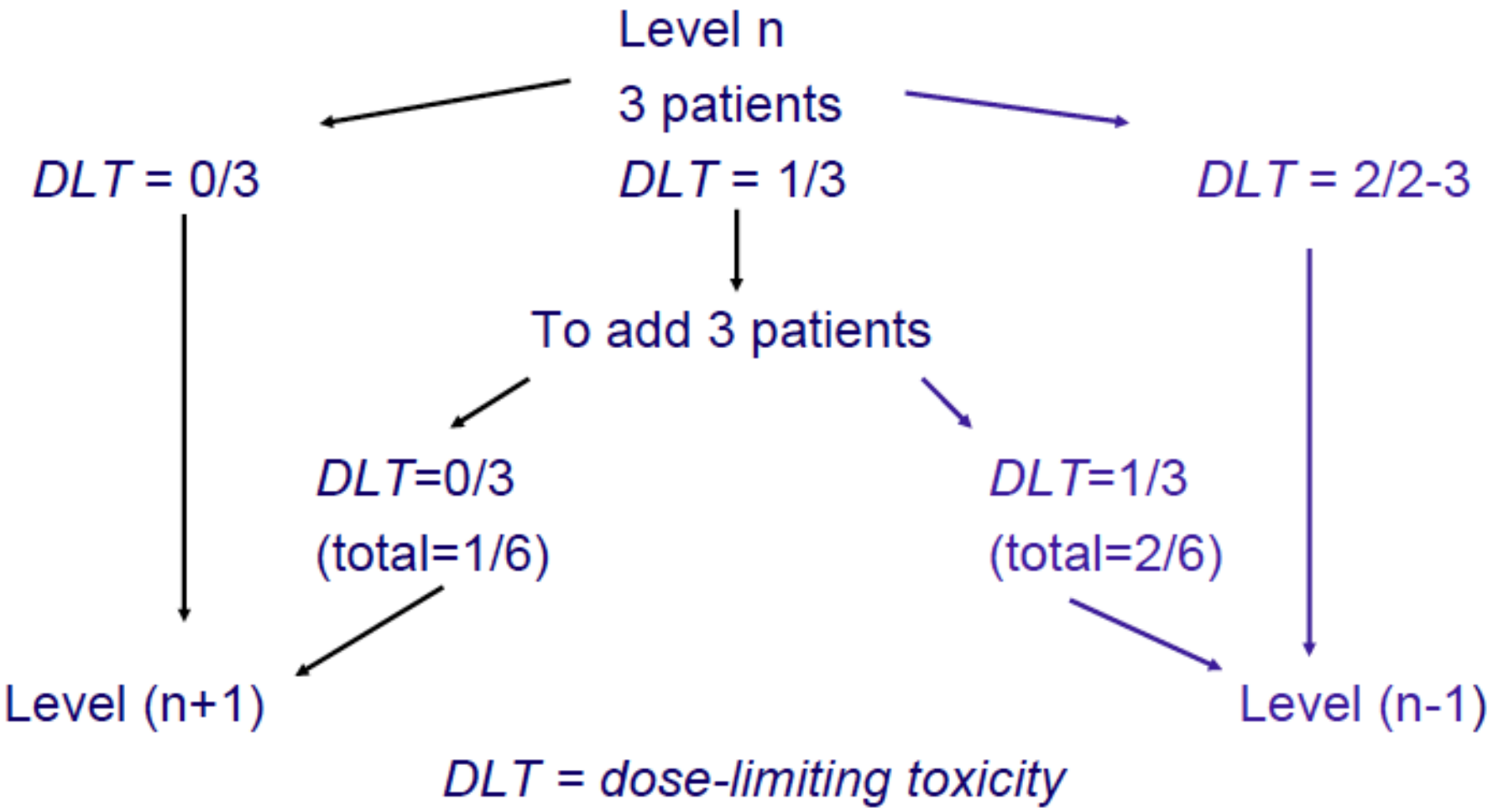
# Statistical designs

- Quigley stated that design should aim
  - 1. minimize the number of under-treated patients, that is, patients treated at unacceptably low-dose levels;
  - 2. minimize the number of overtreated patients, that is, patients treated at unacceptably high-dose levels;
  - 3. minimize the number of patients needed to complete the study (efficiency); and
  - 4. respond quickly to inevitable errors in initial guesses, rapidly escalating in the absence of indication of drug activity (toxicity) and rapidly de-escalating in the presence of unacceptably high levels of observed toxicity.

# Statistical designs

- Quigley coined the terms
  - "memoryless or memory" based designs
- Memoryless designs
  - Classical "up and down"
    - Traditional escalation rule or 3+3 design
  - Rolling 6 design

# ‘Classical’ 3+3 Dose Escalation




*DLT = dose-limiting toxicity*

# Statistical designs

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Shortening the Timeline of Pediatric Phase I Trials: The Rolling Six Design

*Jeffrey M. Skolnik, Jeffrey S. Barrett, Bhuvana Jayaraman, Dimple Patel, and Peter C. Adamson*

**Results**

In twelve completed historical studies, the median time to study completion was 452 days (range, 220 to 606 days); number of evaluable participants enrolled was 22 (range, 11 to 33), and DLTs occurring per study was three (range, 0 to 5). In 1,000 study simulations, in which the average time to new patient accrual was 10 days, the average ± standard deviation (SD) time to study completion was 294 ± 75 days for the rolling six design versus 350 ± 84 days for the 3 + 3 design, whereas the number of DLTs per study was the same (average ± SD, 3.3 ± 1.1 *v* 3.2 ± 1.1 for the rolling six and 3 + 3 designs, respectively).

**Conclusion**

The rolling six design may significantly decrease the duration of pediatric phase I studies without increasing the risk of toxicity. The design will be tested prospectively in upcoming Children's Oncology Group phase I trials.

# Statistical designs

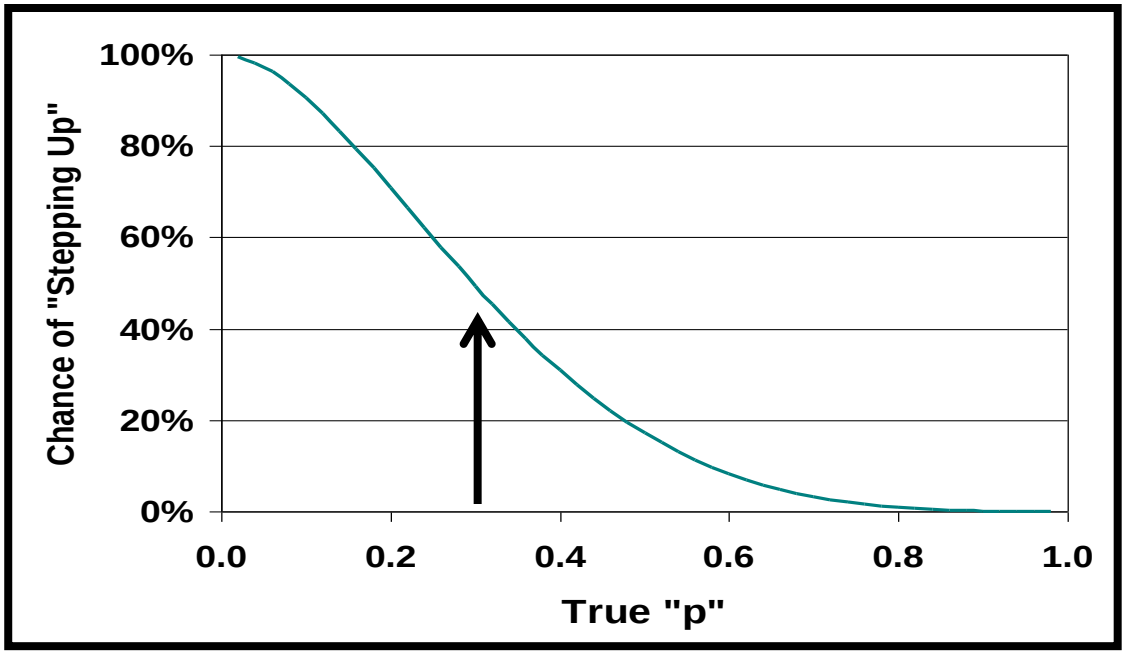
- 3+3 design
  - Cohorts of 3
  - Need toxic data from all 3
  - If 0/3 DLT
    - Next dose level
  - If 2/3 DLT= MTD
    - De-escalate so 6 at MTD
  - If 1/3 DLT
    - Expand to 6
    - If 1/6 DLT next level
    - If 2/6 DLT= MTD
    - replace inevaluable patient
- Rolling 6's
  - Cohorts of 6
  - Need toxic data from 3
  - If 0/3 DLT
    - Next dose level
  - If 2/3-6 DLT= MTD
    - De-escalate so 6 at MTD
  - If 1/3 DLT or awaiting data
    - Continue the dose up to 6
    - replace inevaluable patient

# Fixed dose (memoryless) designs

**PROs** of Conventional 3+3 Designs:

- Simple and intuitive algorithm
- Easy to implement and monitor – requires no computer program
- Familiar to many clinicians

However, the method has been criticized for treating many patients at low, ineffective doses and not producing a good estimate of the MTD.




For example, with a true 30% chance of a toxicity, there is still a 50% chance of “stepping up” to the next dose.

Hence, unsafe doses may be advanced to future trials.

# Adaptive (memory) based designs

Adaptive dose finding methods offer more efficient ways to learn about dose response.

Most common approach is Continual Reassessment Method [CRM - See Garrett-Mayer (Statistics in Medicine, 2006) for an excellent tutorial].

- Originated as a Bayesian method for phase I cancer trials of cytotoxic agents.
- Assumes a particular model (such as logistic function), and probabilities of both efficacy and toxicity increase with increasing dose
- Assignment of doses converges to the MTD.

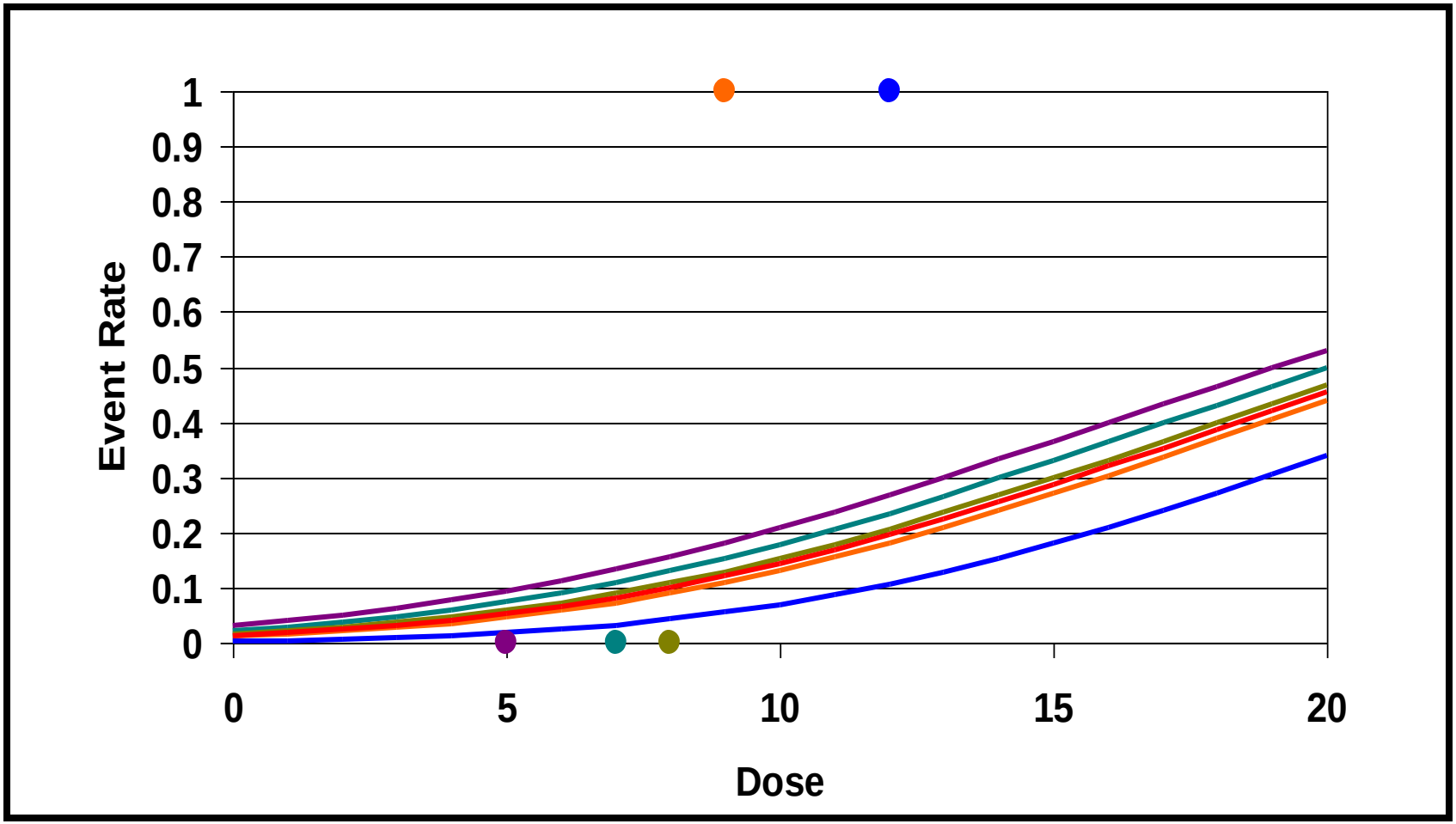
## Steps for implementing CRM:

1) Begin with assumed a priori dose-toxicity curve and a chosen target toxicity rate
2) Assign first subject(s) dose most likely to be associated with target toxicity level
3) Updated dose-toxicity curve is refit (shifted slightly up or down) depending on whether or not first subject(s) experienced a DLT
4) Next subject assigned dose closest to target toxicity level based on updated curve
5) Continue until some pre-defined stopping criteria are met

For example, consider the following curve:


If target level of toxicity is 10%, then dose level 5 would be the optimal starting dose.

# An example of how the CRM might work:



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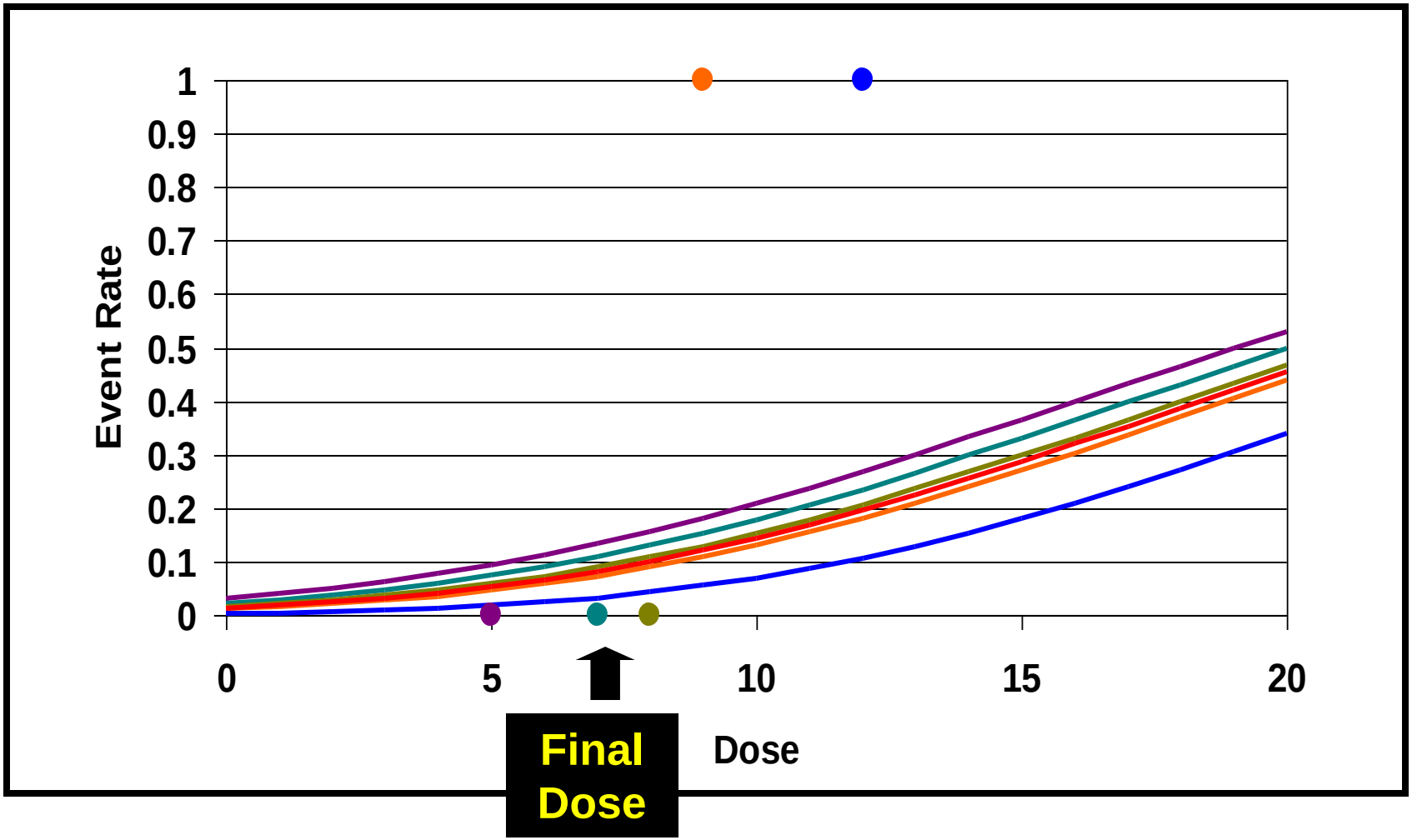



Thanks to George Howard (University of Alabama at Birmingham) for Example

# Adaptive (memory) based designs

**PROs** of CRM:

- "Learns" from information gained at early time points in the study – all participants studied contribute to the estimated dose.
- Generally more efficient/safer than 3+3 design
  - Can more accurately estimate the MTD as compared to standard 3+3 designs
  - More likely to treat participants at doses around the MTD
  - Less likely to treat participants at ineffective doses
  - Less likely to treat participants at toxic doses – tends to incur fewer dose-limiting toxicities.

# Adaptive (memory) based designs

**CONs** of CRM:

- Implementation requires a substantial collaboration between the investigator and statistician
- Mathematical and statistical complexities make it difficult for many clinical investigators to understand.
- Properties must be assessed via simulation.
- Safety concern with original CRM: Large dose escalations can occur early based on limited information.

# Adaptive (memory) based designs

Several modified CRM approaches have been developed to address these concerns:

- Always start at lowest dose level under consideration
- Enroll 2-3 patients in each cohort
- Any given dose escalation cannot increase by more than one level.

# Toxicity determination & definitions

- Non-clinical toxicity profile from animals
  - Often very little "juvenile toxicity data"
- Adult toxicity data
- From available toxicity data can consider
  - Range of toxic effects & assessments required
  - Scheduling of assessments
  - Inclusion/ exclusion criteria
  - Concomitant supportive Rx
  - Design of data collection for Adverse Events (AEs)
  - Consideration of how/when to determine causality

# Toxicity determination & definitions

## Common Terminology Criteria for Adverse Events (CTCAE) version 4

Contents



### BLOOD/BONE MARROW



| | | Grade | | | | |
|---|---|---|---|---|---|---|
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Bone marrow cellularity | Bone marrow cellularity | Mildly hypocellular or ≤25% reduction from normal cellularity for age | Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age | Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age | — | Death |
| CD4 count | CD4 count | <LLN – 500/mm$^3$<br><LLN – 0.5 x 10$^9$ /L | <500 – 200/mm$^3$<br><0.5 – 0.2 x 10$^9$ /L | <200 – 50/mm$^3$<br><0.2 x 0.05 – 10$^9$ /L | <50/mm$^3$<br><0.05 x 10$^9$ /L | Death |
| Haptoglobin | Haptoglobin | <LLN | — | Absent | — | Death |
| Hemoglobin | Hemoglobin | <LLN – 10.0 g/dL<br><LLN – 6.2 mmol/L<br><LLN – 100 g/L | <10.0 – 8.0 g/dL<br><6.2 – 4.9 mmol/L<br><100 – 80g/L | <8.0 – 6.5 g/dL<br><4.9 – 4.0 mmol/L<br><80 – 65 g/L | <6.5 g/dL<br><4.0 mmol/L<br><65 g/L | Death |

# Toxicity determination & definitions

- Dose limiting Toxicity
  - This is determined prior to trial
  - May vary according to agent, malignancy and population
  - Usually any non-haematological grade 3 CTCAE
    - Exceptions ? N&V (may allow prophylaxis)
  - Haematological toxicity
    - If agent is known to cause myelosuppression
    - Grade 4 CTCAE allowed but duration/ recovery defined
    - This may vary for leukaemia vs solid tumour trials

# Toxicity determination & definitions

- Dose limiting Toxicity
  - Need to define the evaluation period
  - Usually 1-2 courses but note with targeted agents cumulative toxicity and tolerability are important!
- Non-DLT AE/ AR
  - Obviously these characterise toxicity profile
  - ? Cumulative/ Late
  - Consider possible paediatric specific issues
    - Effects on development/ maturation e.g. growth
  - Need to consider if Non-DLT
    - May influence tolerability

# Specific Phase I challenges

- Specifically “targeted” agent
  - Should the population be selected?
    - Agent may not act as expected “Off target” effects
    - On tumour type
    - On target identification
    - Consider “enriching” population at RPII dose & following PD proven proof of mechanism

# Specific Phase I challenges

- If tumour specific phase I challenges
  - E.g. CNS tumours
    - Existing/ new tumour related neurological AE's
    - CSF/ BBB penetration
  - E.g. Leukaemia
    - Patients usually very heavily pre-treated (post-BMT)
    - Very quick "doubling time"
    - Myelosuppression

# Specific Phase I challenges

- Multiple agent combination Phase I studies
  - Data available from adult combination?
  - Data from single agent Phase I
  - Toxicity profiles “overlapping”
  - PK Interactions?
  - Starting doses
  - Dose escalation
    - Can model using dose/ toxicity diagrams
    - May depend on action (targeted vs. non)

# Practical issues

- Burden of assessments on patient
  - Number of interventions e.g. scans, blood tests and volumes, painful procedures
- Patient information
  - Consent and assent
  - During the trial
- Complexity/ timings of sample and investigation collection

# Pitfalls

- Formulation- at this stage maybe only adult formulation e.g. tablets/ capsules and doses available
  - Maybe difficult to deliver ideal dose cohorts for wide range of ages/ body size!
- New paediatric formulations
  - Need to consider palatability, stability for specific child populations e.g. can drug go down NG tube?

# Pitfalls

- We tend to not explore multiple schedules and simply take the adult schedule!
- Lack of translational biology means we may not be able to interrogate responders vs non-responders and reject sensitive subgroups

# Pitfalls/Opportunities

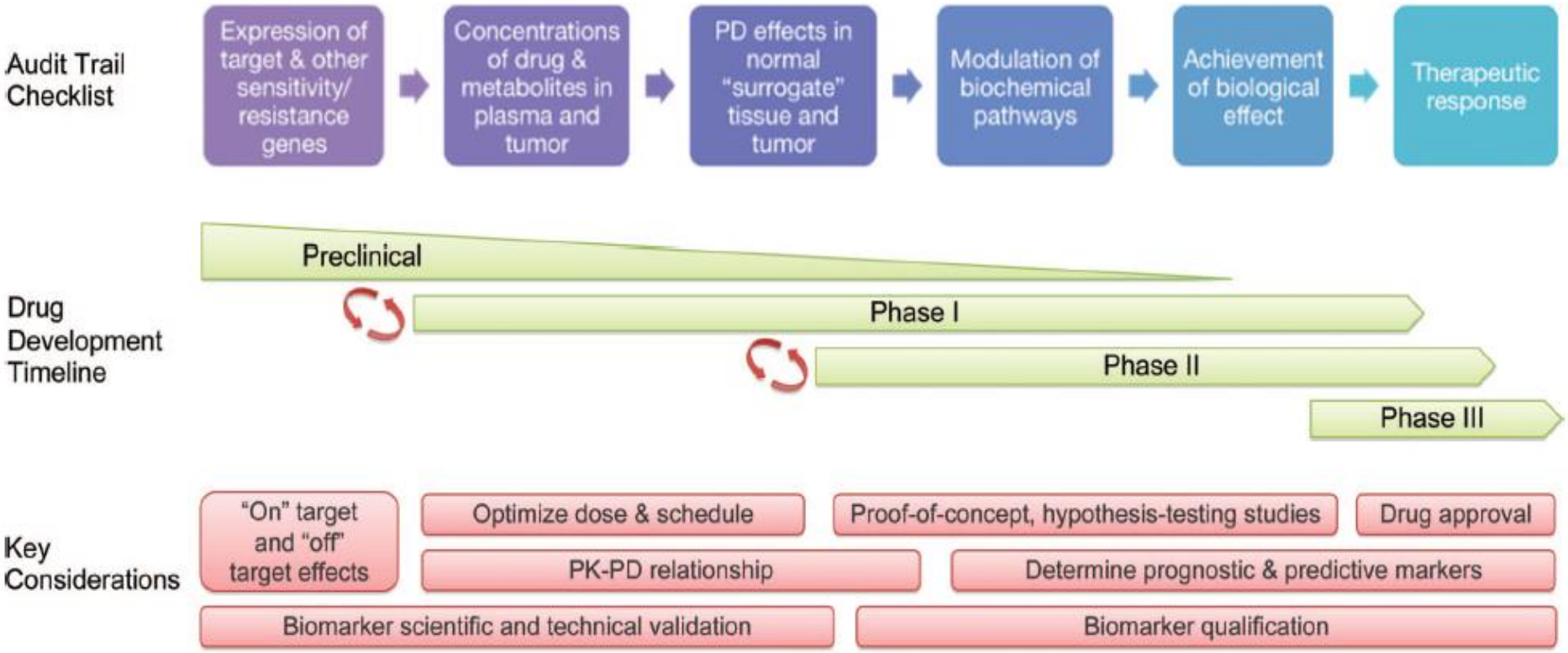
- If starting dose is 100% adult and not likely to reach an MTD
  - When to stop? PK or PD based use scaled adult RP2D
  - Not many patient in dose escalation
  - Not enough for PK/ toxicity age subsets
  - Not enough for varying tumour subtypes
- Dose expansion cohorts
  - Allows extra PK/PD & preliminary activity data
- Seamless phase I/II study
  - Formally powered preliminary activity/ efficacy

# Biology-led clinical trials of targeted drugs

- Clinical trials for targeted drugs should be led by the biology & the clinical hypothesis.
  - **Hypothesis-testing** and **Biomarker-led**.
  - A drug acting on a specific molecular target is efficacious in patients with a particular type of genetic aberration.
  - Shift away from patient selection based on anatomical site & histology to stratification based on genomic aberrations.

# Pharmacological Audit Trail





# Classification of Biomarkers

- Risk Biomarkers *(patient selection)*
  - Prognostic
  - Predictive
- Pharmacodynamic (target modulation/ treatment effect)
  - Proof of mechanism
  - Proof of concept
  - Toxicity
- Biological progression marker (post-treatment monitoring)
- Surrogate end-point (correlated with overall survival)

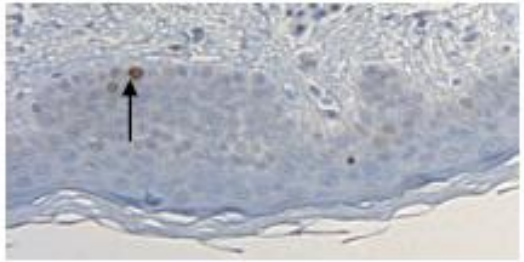
# Types of Biomarkers

- Direct
  - Tumour biopsy
  - CSF cytology?
- Surrogate
  - Blood
    - Traditional (serum & PBMC)
    - Emerging (circulating tumor cells, free nucleic acid, proteomic and metabolomic markers)
  - Skin & hair follicles
  - Imaging biomarkers

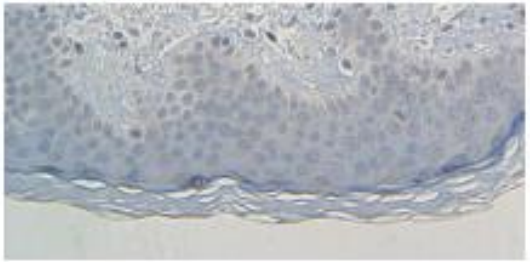
# PD biomarkers in skin biopsies from AT9283/0001

Immunohistochemistry of skin biopsies
(Dose level 6 mg/msqud/day)

Pt 02003
C1H0



C1H46



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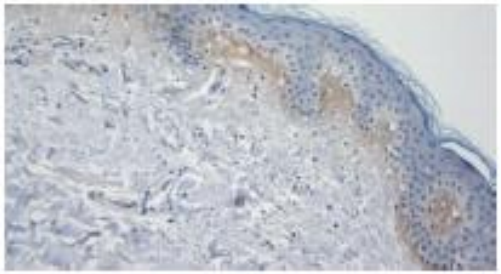
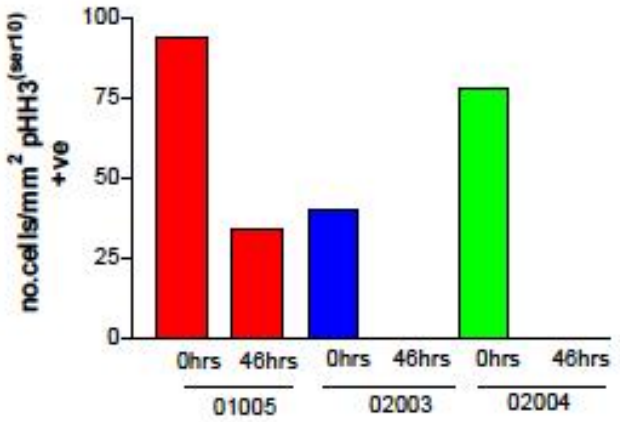
C1H0

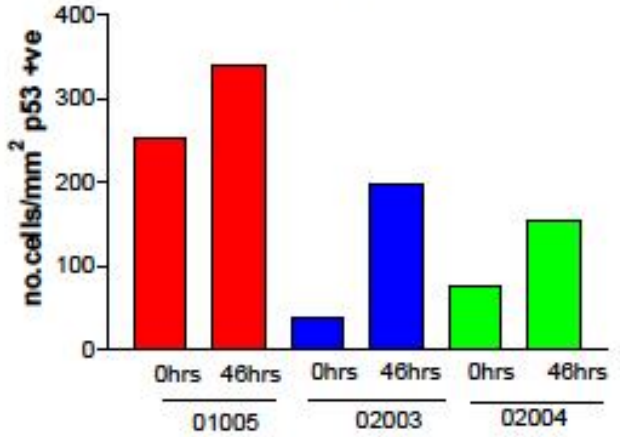


C1H46

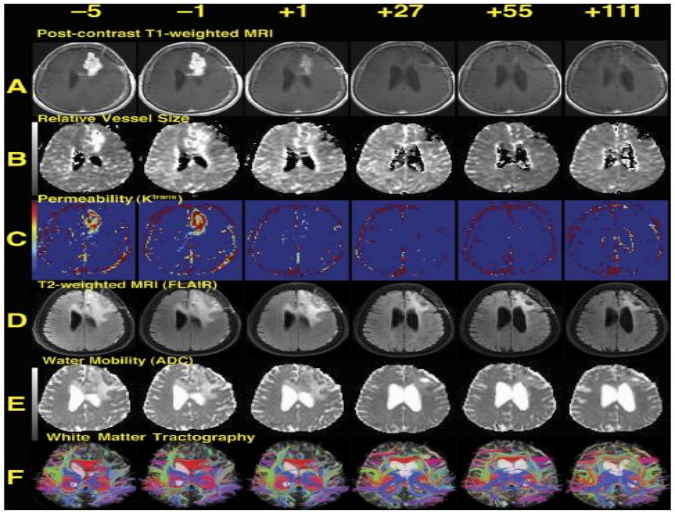
No. cells/mm$^2$ positive for pHH3$^{(ser10)}$
Cohort III (18mg/m$^2$/72hrs)

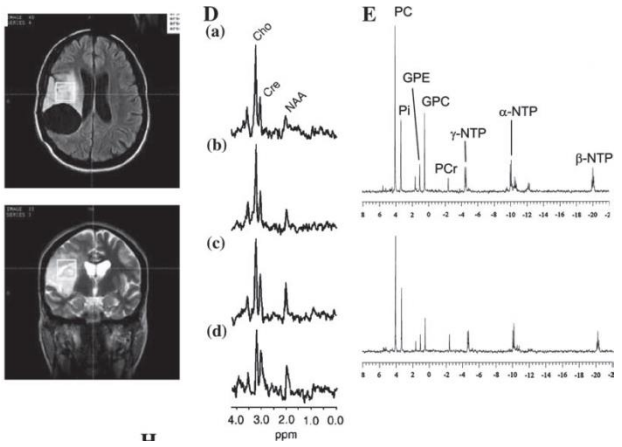


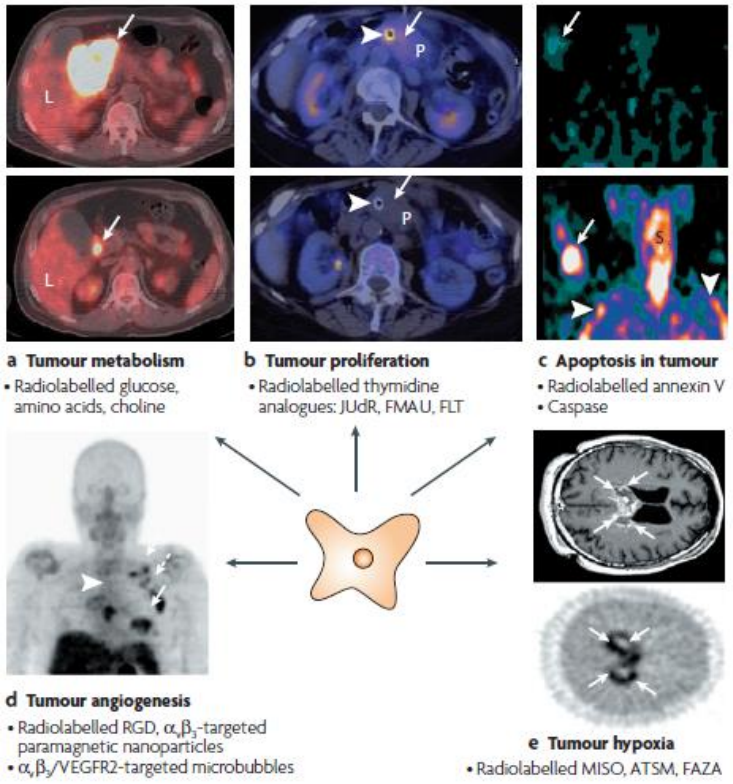

No. cells/mm$^2$ positive for p53
Cohort III (18mg/m$^2$/72hrs)



# Imaging Biomarkers



# Combination Studies

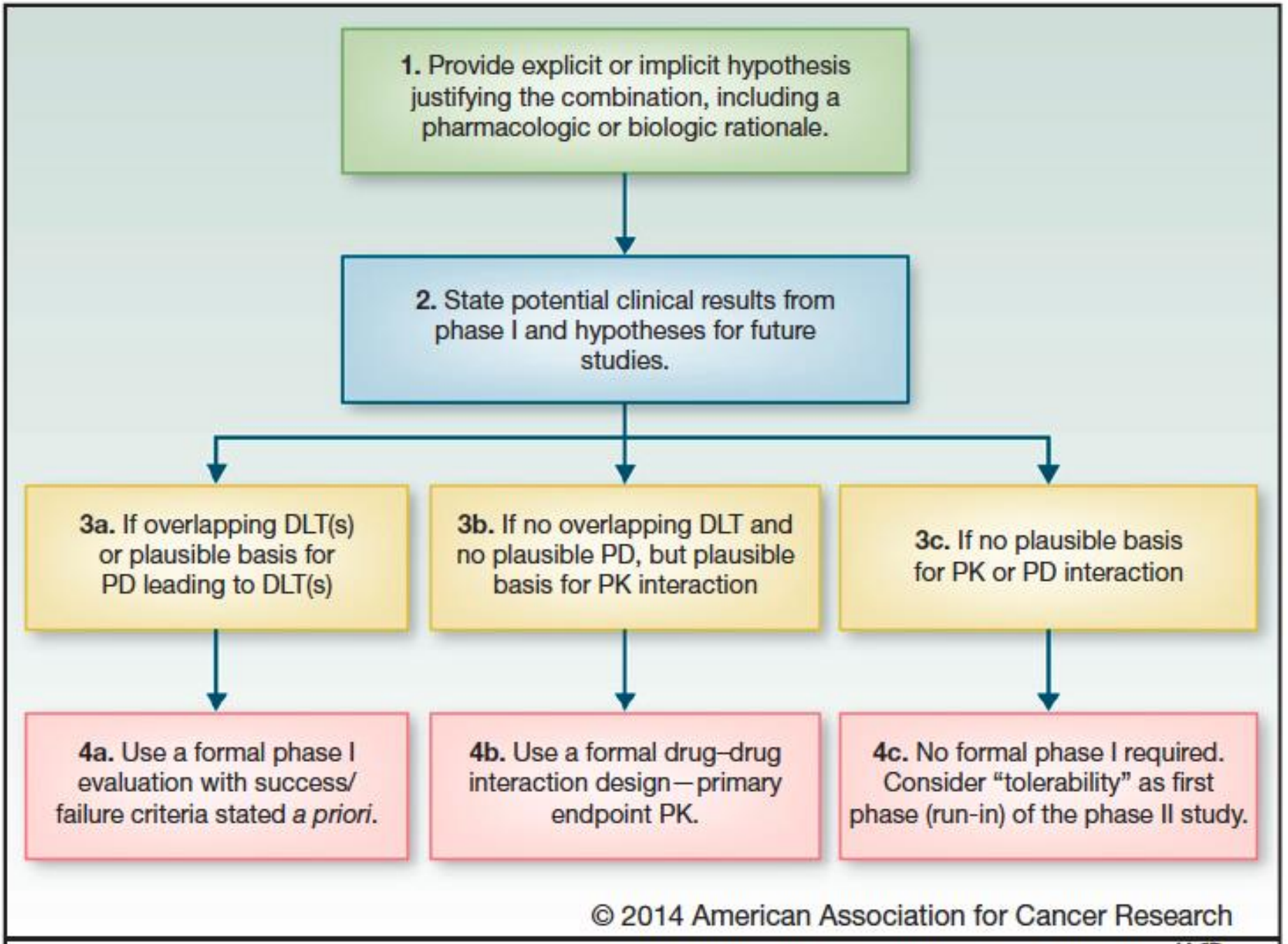
- Very few drugs will cure cancer as single agents!
- Combination could be with existing SOC
  - Cytotoxic chemotherapy
  - Radiotherapy
  - Targeted agent(s) based on scientific/ pre-clincal rationale

# Design of Phase I Combination Trials: Recommendations of the Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee

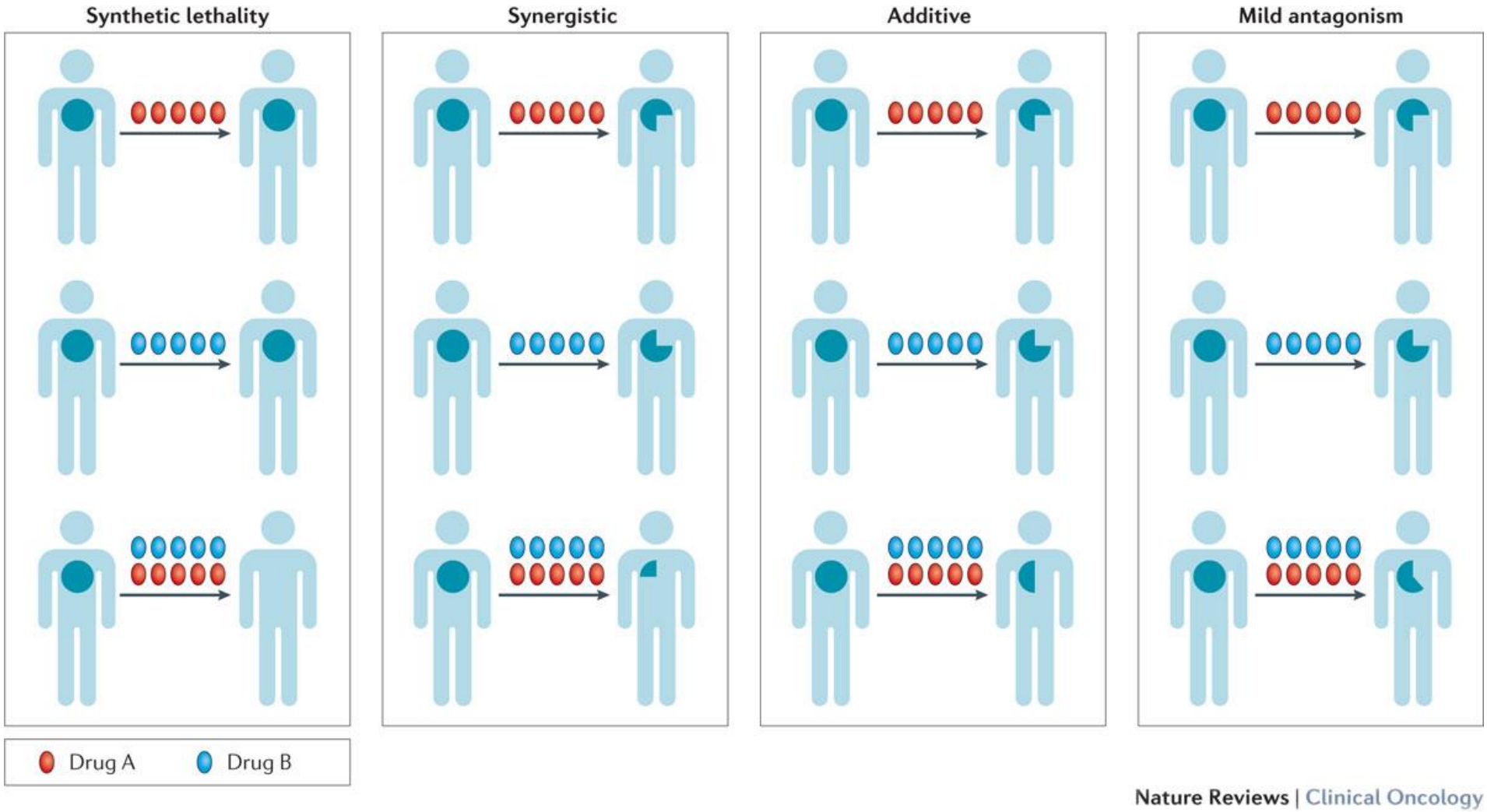
Channing J. Paller[1], Penelope A. Bradbury[11], S. Percy Ivy[2], Lesley Seymour[11], Patricia M. LoRusso[3], Laurence Baker[4], Larry Rubinstein[2], Erich Huang[2], Deborah Collyar[5], Susan Groshen[6], Steven Reeves[2], Lee M. Ellis[7], Daniel J. Sargent[8], Gary L. Rosner[1], Michael L. LeBlanc[9], and Mark J. Ratain[10]



AACR American Association for Cancer Research

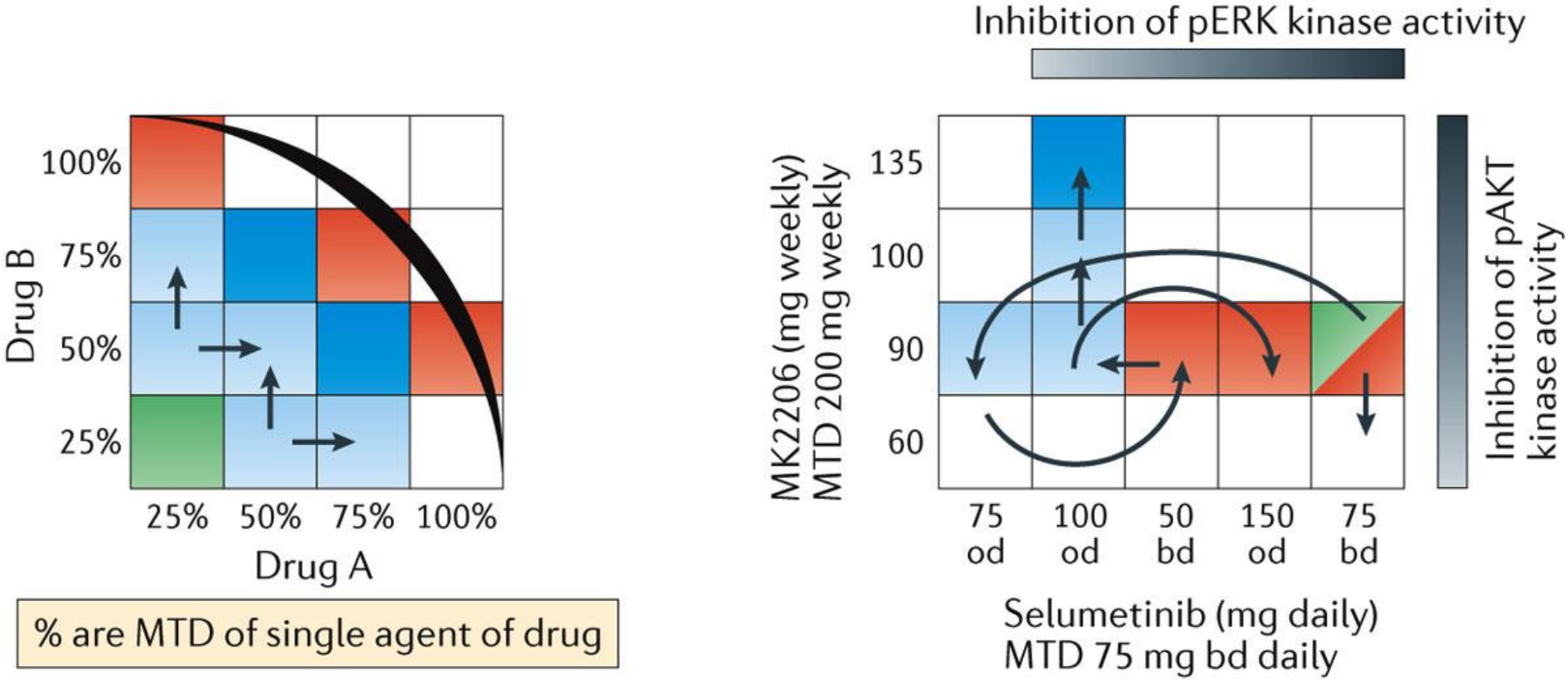


# **Figure 1** Clinical impact of drug combinations on the tumour




Lopez, J. S. & Banerji, U. (2016) Combine and conquer: challenges for targeted therapy combinations in early phase trials
*Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.96

# **Figure 2** The challenge of optimizing drug dosing in combination regimens

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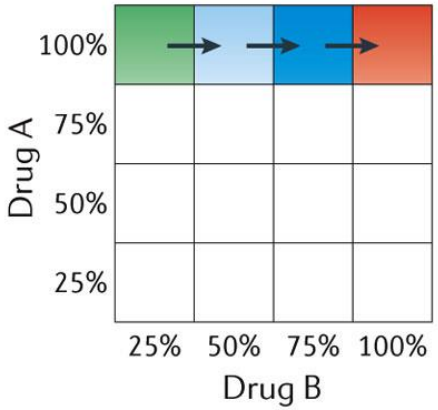
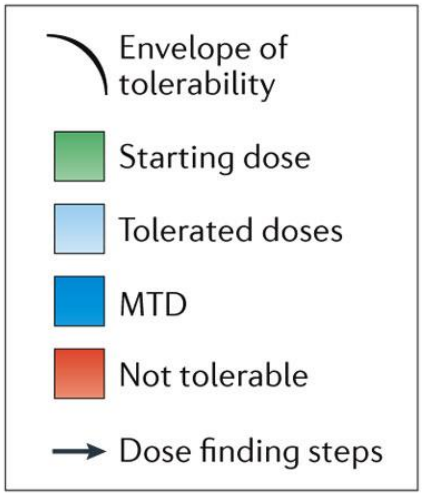
# **Figure 2** The challenge of optimizing drug dosing in combination regimens

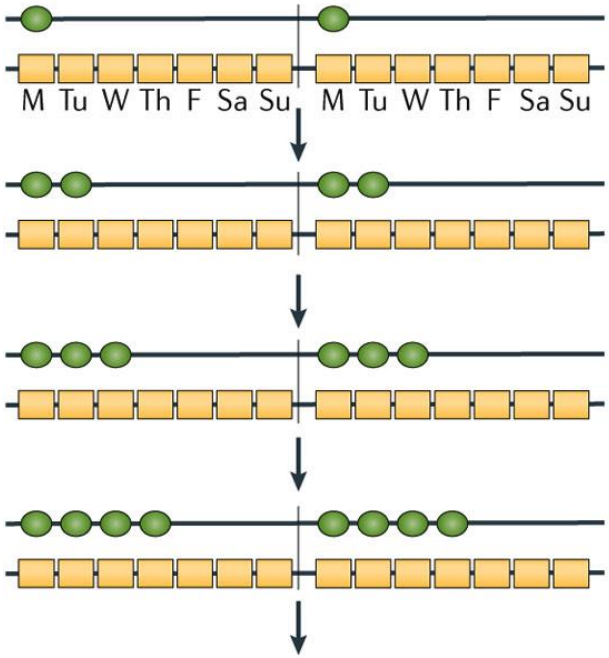
**b** **Dose finding guided by optimal target inhibition of combinations**



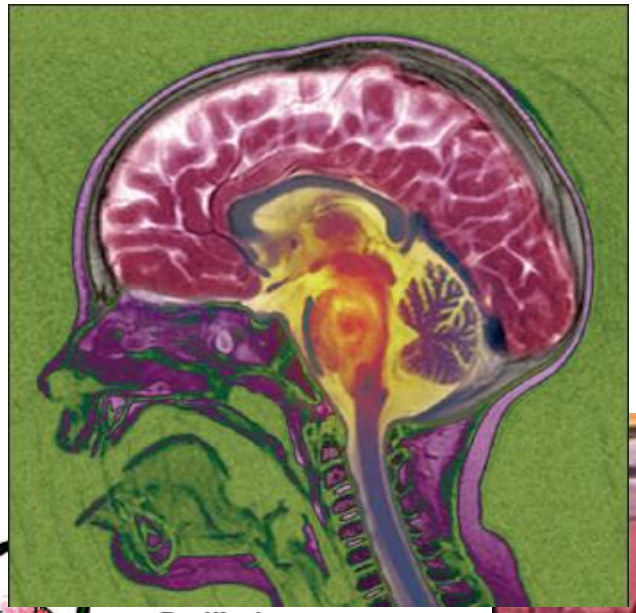

% are OBD of single agent of drug

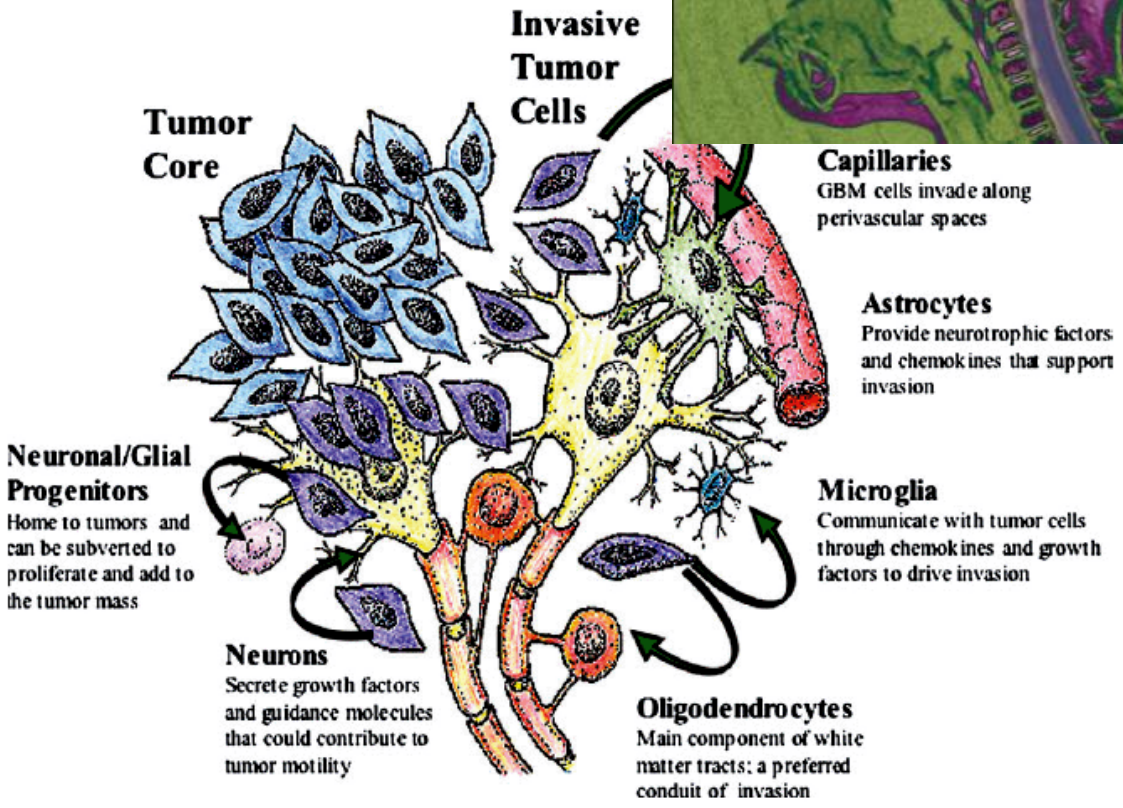


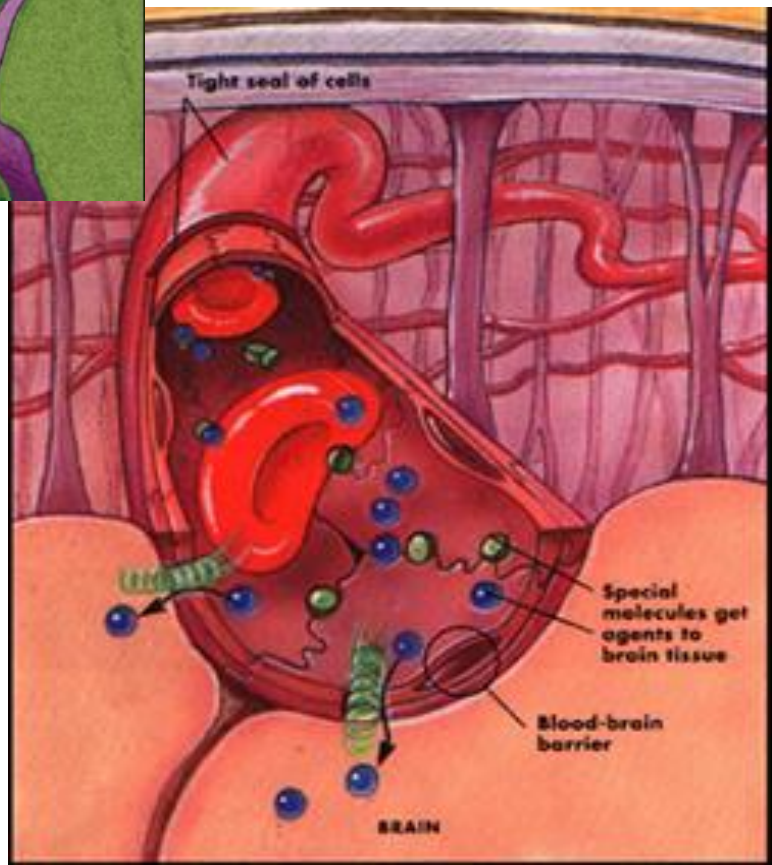

**c** **Novel dose-escalation strategy using creative scheduling to optimally hit both targets**




# Poor Drug Delivery

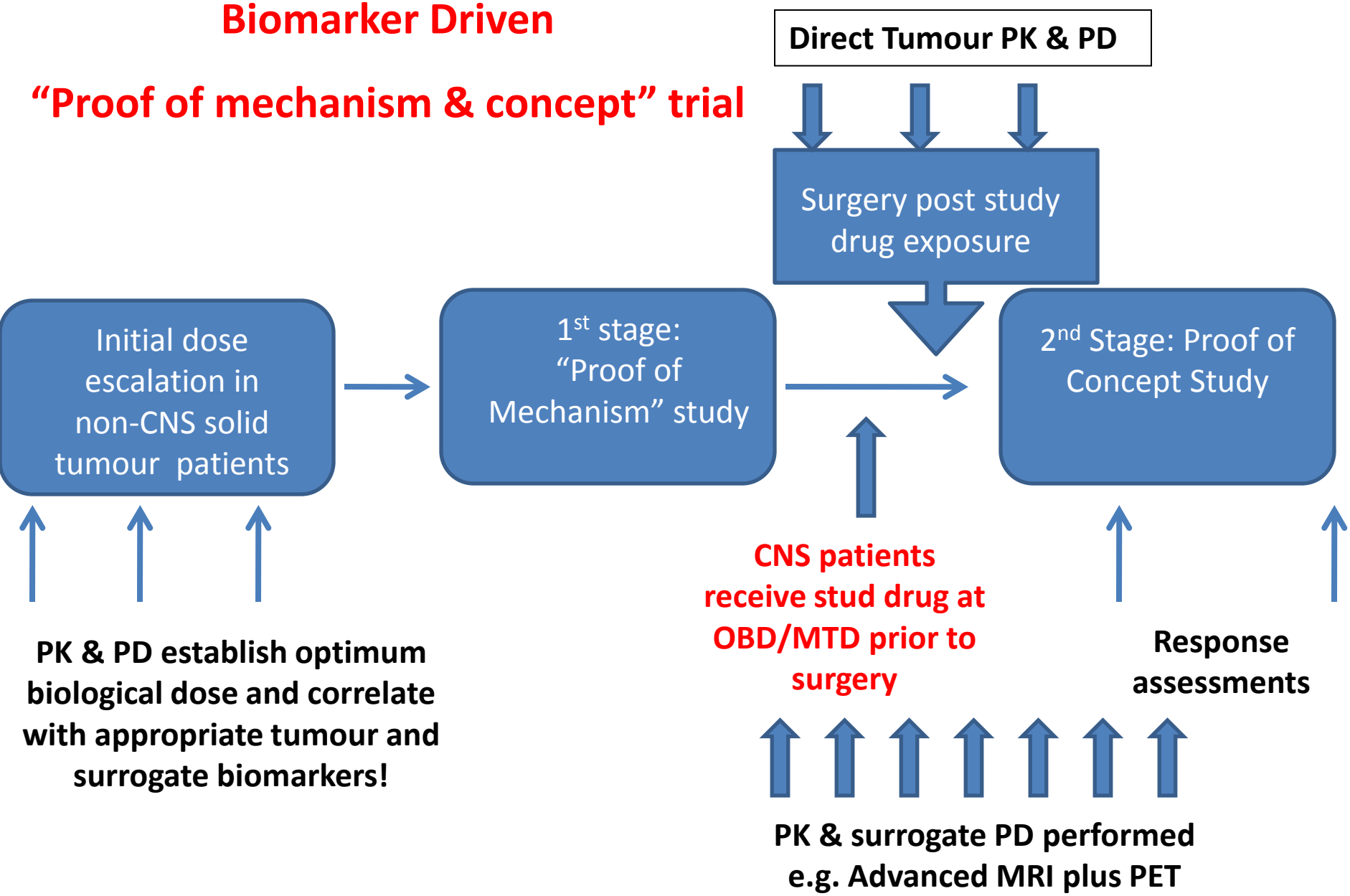




# Biomarker Driven

## "Proof of mechanism & concept" trial



# Questions?