NCIC CTG New Investigator Clinical Trials Course

Phase I Trials

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Educational Objectives

- Understand the goals of a phase I trial
- Be familiar with the concepts of dose limiting toxicity, recommended phase II dose
- Describe some different phase I clinical trial designs
- Discuss considerations when designing a phase I combination clinical trial

Purpose of the phase I trial

- Critical first step in cancer drug development
  - First in human
    - First time a new class of drugs is evaluated
    - First time a specific drug has been evaluated, although not first in class
  - Phase I to evaluate a combination of drugs
    - Marketed- marketed
    - Investigational- marketed
    - Investigational-investigational
  - Drugs in combination with radiation

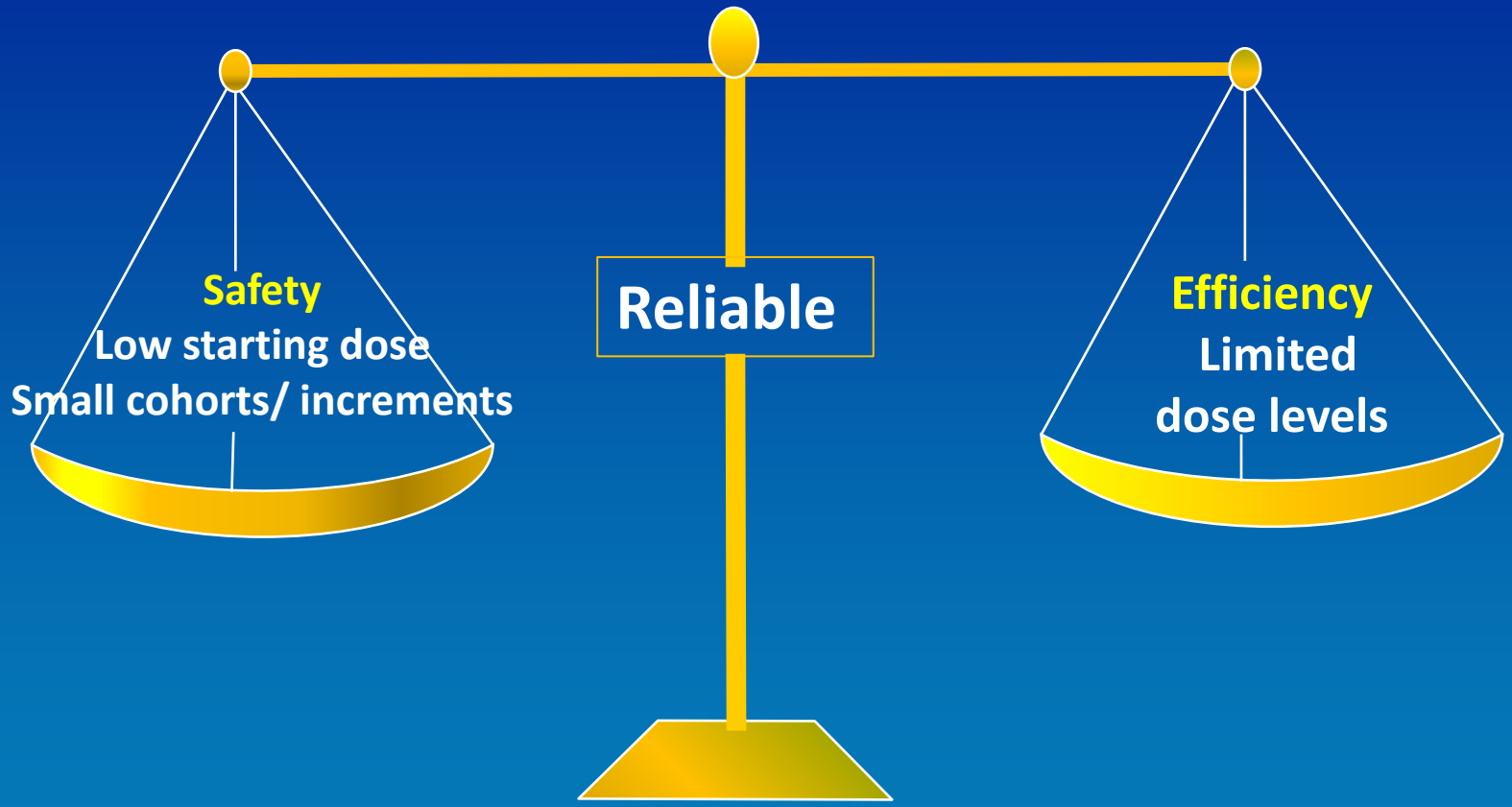
Common endpoints

- **Primary**
  - Determine recommended dose of a new agent (regimen) for further study
- **Secondary**
  - Evaluate toxicity
  - Determine pharmacokinetics
  - Evaluate preliminary evidence of anti-tumour activity
  - Evaluate relationship between dose/ PK and effects on toxicity or PD effects (molecular drug effect in tissues)

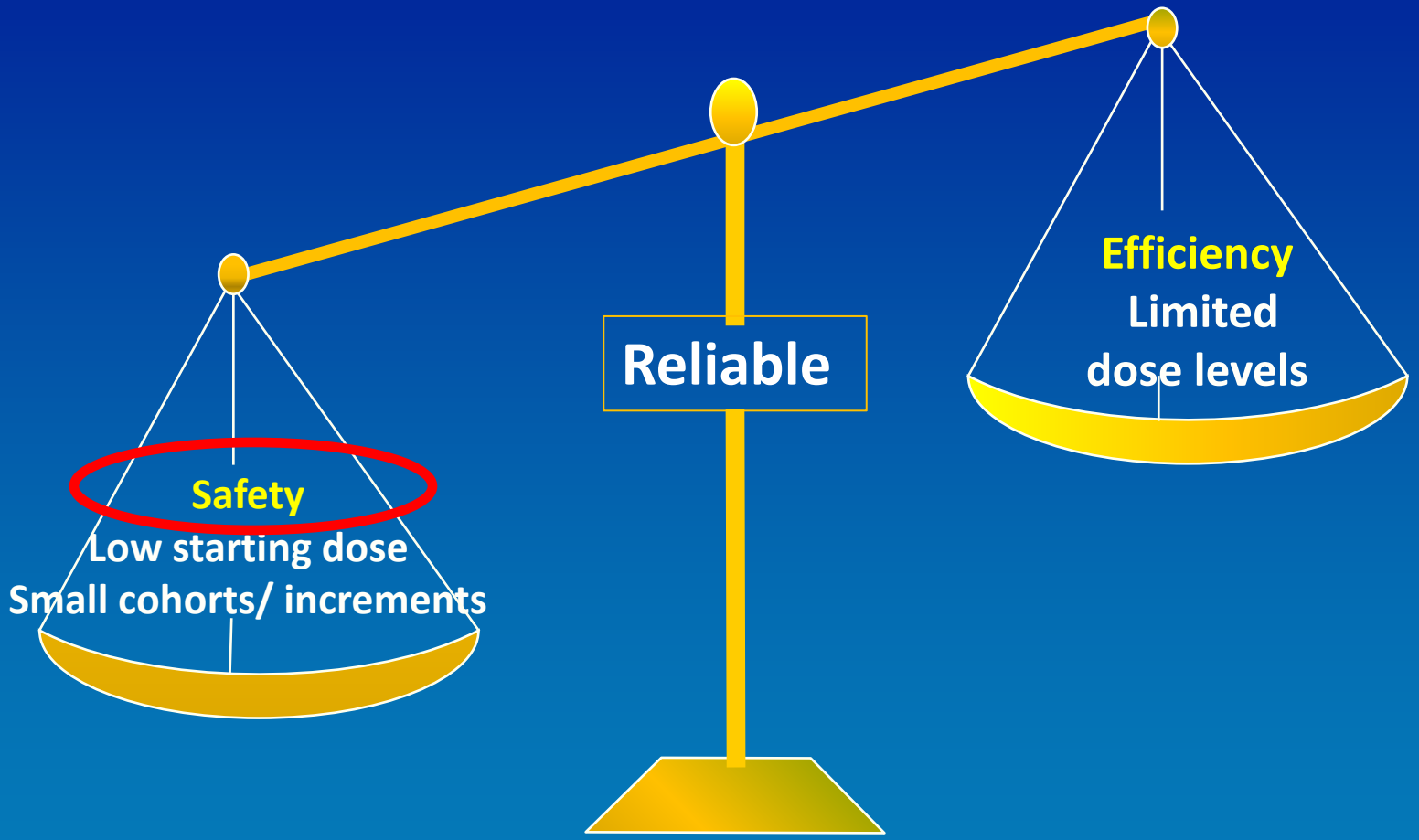
Definitions

- **Dose limiting toxicity (DLT)**
  - Occurrence of a toxicity of a severity or consequence that may limit dose escalation
- **Maximum tolerated dose (MTD)**
  - Dose at which a pre-specified number of patients exhibit a DLT leading to the halting of further dose escalation
  - Dose level below the dose level at which the pre-specified number of DLTs occurred halting of further dose escalation
- **Maximum Administered Dose (MAD)**
  - Highest dose administered
- **Recommended Phase II Dose (RP2D)**
  - Dose recommend for further study

Perfect design



Perfect design



Patient Population

- **First in human trials usually conducted in cancer patients for whom no curative or standard treatment options remain**
  - Rarely healthy volunteers are used
- **Disease specific phase I**
  - Combination trials when target population for one or more agents may be known
  - Drugs for a specific molecular target

Dose limiting toxicity

- Dose limiting toxicity (DLT)- occurrence of a toxicity of a severity or consequence that may limit dose escalation
- Pre-specified in the clinical trial protocol
- Use a defined grading system for toxicity
  - E.g. Common Terminology Criteria for Adverse Events
    - http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
- Usually based on toxicity that occurs in the cycle 1

Dose Limiting Toxicity- Examples

- **Classic definition**
  - Any grade 3-4 non haematological or grade IV haematological toxicity related to the study drug occurring in cycle 1
- **May include duration or events that occur despite supportive therapy**
  - Grade 4 Neutropenia lasting for more than 5 days
  - Grade 3 diarrhea lasting for >48 hours despite adequate anti-diarrheal therapy
- **For drugs that are dosed frequently e.g daily oral drugs inability to complete a pre-specified proportion of the planned treatment may be included as a DLT**

Challenges of classic DLT definition in era of MTA

- **May be lower grade toxicity but chronic due to more frequent dosing**
  - 50% of patients receiving MTAs experienced worst toxicity after cycle 1 (J Clin Oncol. 2011: 29 (13):1728-35)
- **Moderate / mild toxicity may impact tolerability of a drug**
  - 25% of dose finding studies of MTA included some grade 2 toxicities as dose limiting
  - 10% included dose modifications in definition of DLT
- **Paoletti et al. suggested:**
  - Worsening from baseline
  - Requirement of minimum dose intensity e.g 70%
  - Incorporation of moderate grade toxicities

X Paoletti et al. Europ J Cancer. 2014; (50)

Starting Dose

- **Choice of starting dose depends on type of trial:**
  - **First in human**
  - **Combination**
  - **Immunotherapy**

Starting Dose

- FIH - Determined case by case utilizing all available information
  - E.g. mechanism of action, toxicology data, PK-PD modelling etc
- Use most conservative dose
- Preclinical toxicology studies
  - EMA, FDA recommend new drugs evaluated in rodent and non-rodent species
  - Generally- starting dose is one-tenth of the dose that is lethal in 10% mice
  - If non-rodent species are more sensitive one-six to one-third of the lowest dose that results in any toxicity in more sensitive species should be used
- Immunotherapies have specific recommendations

Starting Dose- combination studies

- Take into account single agent doses and individual toxicities
  - E.g. 50% of MTD and increase one drug at a time
  - OR minimally biologically active dose
  - OR start at full dose of a standard therapy and escalate the novel agent

Designs

- **Core elements**
  - Safe starting dose
  - Sequential dose escalation in small cohorts
- **Designs**
  - Rule based
    - 3+3 design classical design
  - Model based
    - Continual reassessment design
- **Biological outcome measures**

Dose escalation

1170-1250

Fibonacci series

0, 1, 1, 2, 3, 5, 8, 13, 21, 34

Dose levels

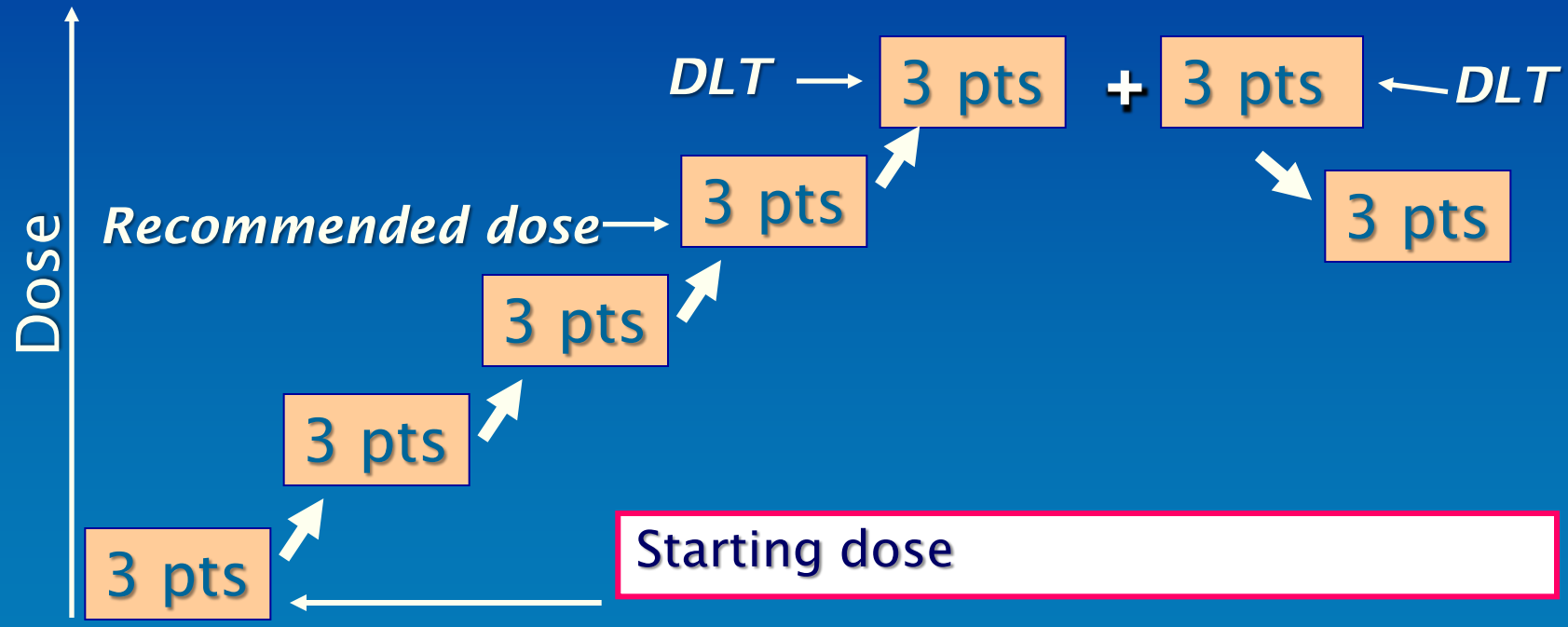
Absolute dose increases grow larger

Relative dose increases are constant (ie approx 2/3rd larger than prior

In practice modifications generally made

e.g. make relative increments smaller at higher dose levels- 100%; 66%; 50%; 40%; 33% (Modified Fibonacci Series)

Phase I trial design: standard 3+3 design



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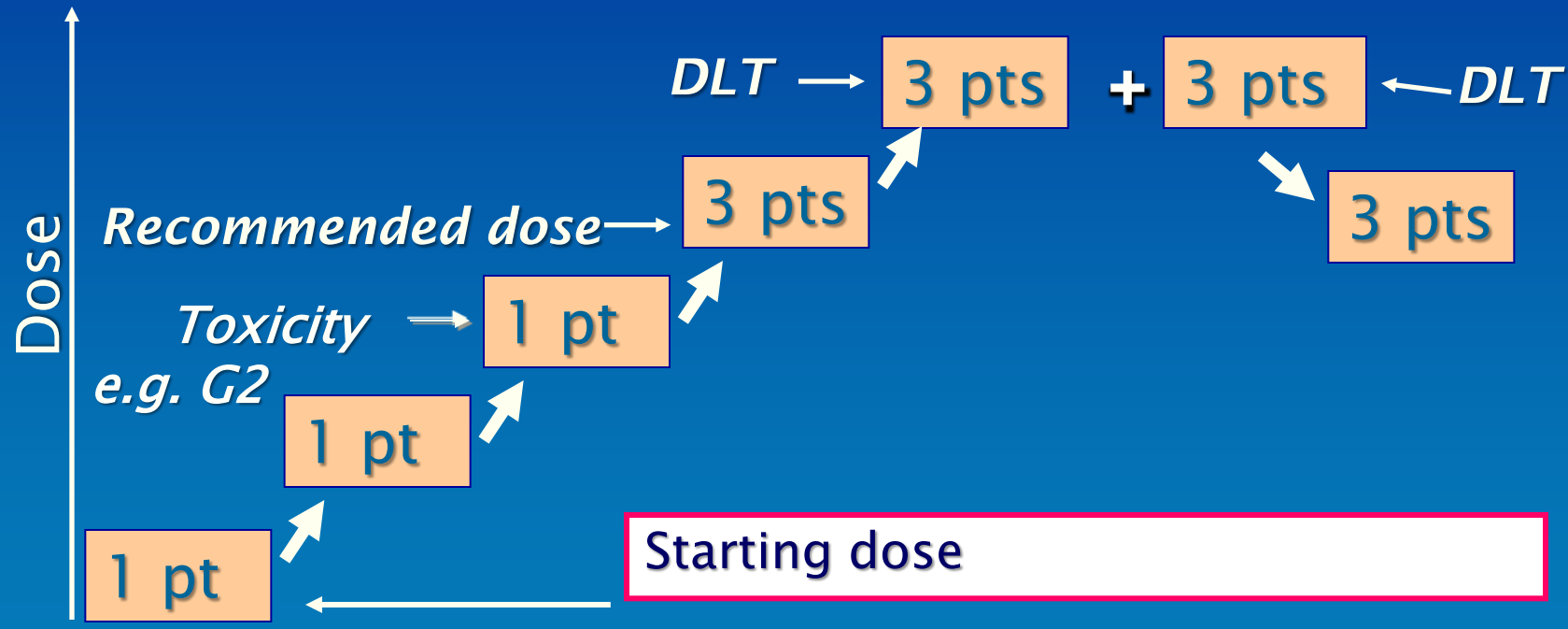
Eisenhauer et al.

Classic Design- Potential Disadvantages

- Dose escalation may require multiple dose escalation steps- slow and many patients may be treated at sub-therapeutic doses
- Few patients treated at MAD potentially leading to uncertainty about the RP2D
- Concern that may not be ideal design for molecularly targeted therapies

Phase I trial design: accelerated titration



Rolling Six

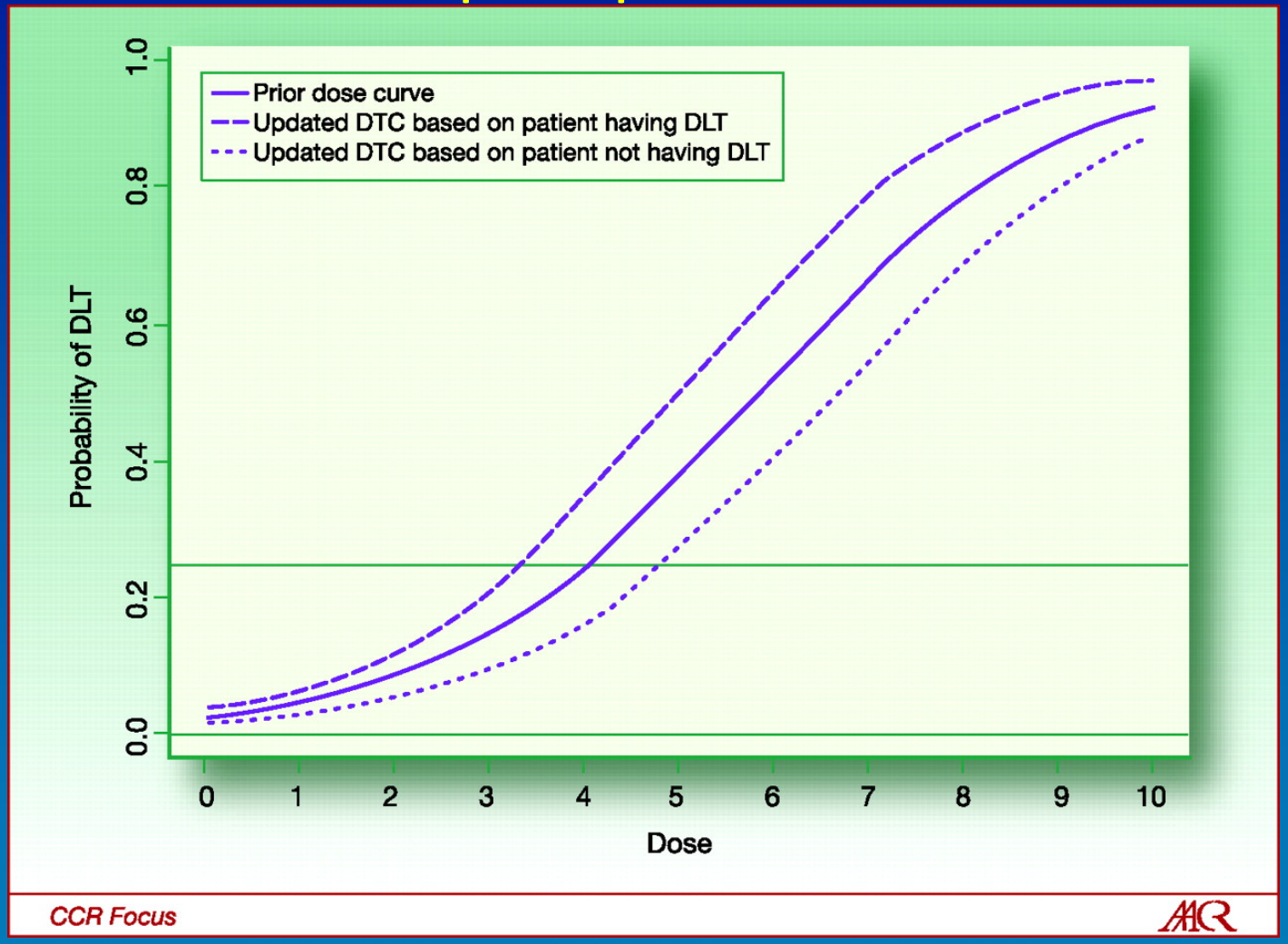
- Enroll 2-6 patients on a dose level
- Patients enrolled based on:
  - Number currently enrolled
  - DLTs
  - Number of patients that have not completed the evaluation period

Model Based Design- Continual Reassessment Method

- Principle- each patient should be allocated to the dose closest to estimated MTD (e.g. dose where 33% patients experience DLT)
- Before trial starts an initial estimate (using existing pre-clinical or clinical data) is made of the probabilities of a DLT occurring as a function of dose
- The determination of the dose for the next patient enrolled is based on toxicity data from previously enrolled patients
  - First patient treated at the dose level thought to be MTD
  - Use data from the patient to update the estimate of the probability of a DLT occurring as a function of dose to define next patient enrolled

O'Quigley et al. 1990

Theoretical Dose Toxicity Curves for continuous reassessment method with one patient per cohort



S. Percy Ivy et al. Clin Cancer Res 2010;16:1726-1736

Other model based designs

- **Adaptions to the continual reassessment method**
  - Treat first patient at the lowest dose level based on animal toxicology data
  - Treat >1 patient at each dose level
  - Constraints on dose increases
- **Escalation with over dose control**
  - Use a Bayesian approach to constrain the proportion of patients that will receive a dose higher than the MTD
- **Isotonic regression**
- **Modified toxicity probability interval**

Which is the most commonly used design?

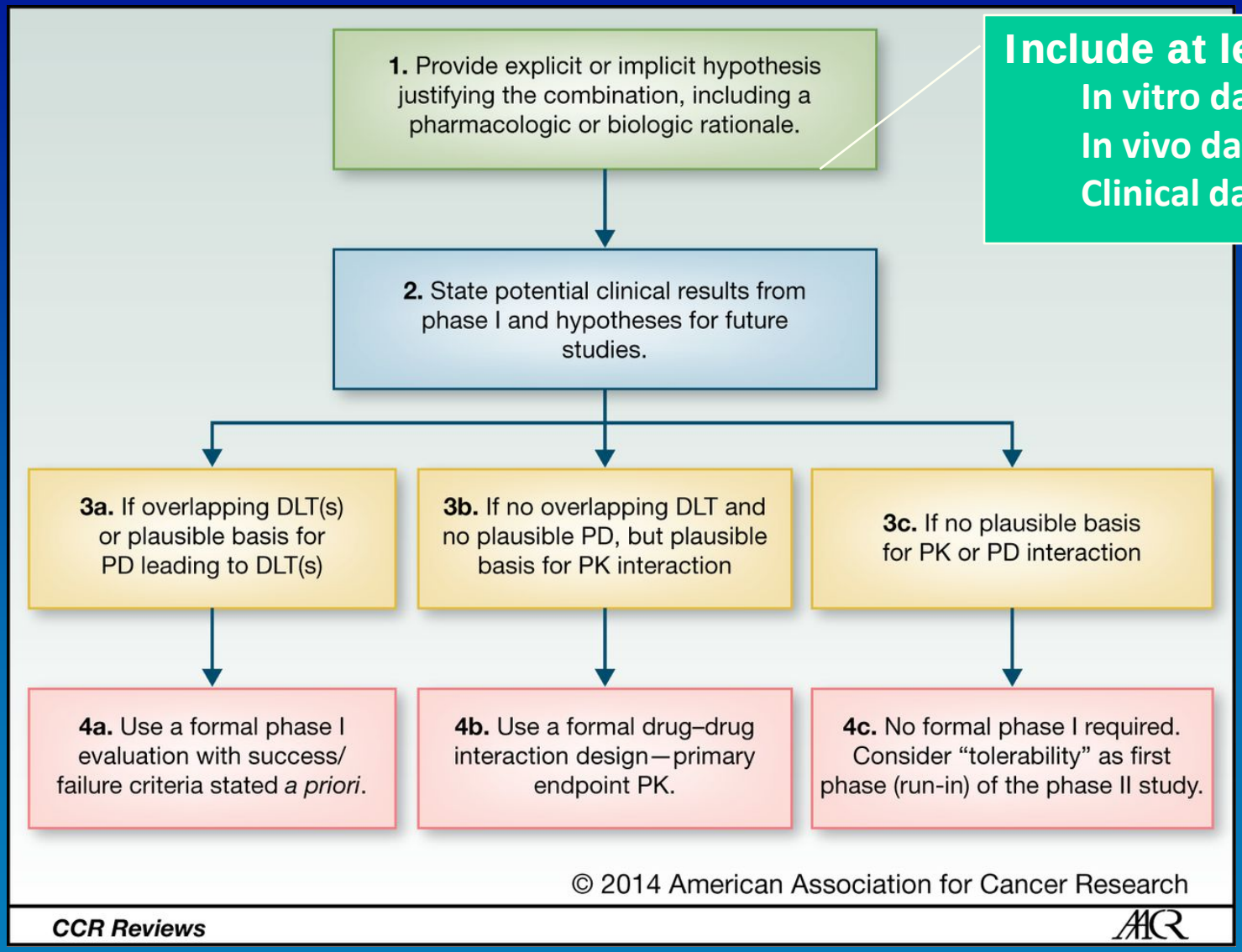
Year	N	Trial Designs	% MTA	Reference
1991-2006	1200	98% 3+3		A Rogatko et al. J Clin Oncol 2007; 25
2007-2008	181	96% 3+3	18%	Le Tourneau et al. J Natl Cancer Inst 2009; 101
2000-2010	155	>60% 3+3	100%	Le Tourneau et al. Eur J Cancer 2011;47

MTA: molecularly targeted agent

Considerations for combination phase I clinical trials

- Combination trials may include
  - Marketed- marketed
  - Investigational-investigation
  - Marketed- investigational
- Considerations
  - Is a phase I trial required
  - What is the optimal design

Process for determination of the phase I combination trial design



Channing J. Paller, P Bradbury et al. Clin Cancer Res 2014;20:4210-4217

Expansion Cohort

- Phase I trials have small sample sizes, and few patients may have been treated at the proposed RP2D – uncertainty
- Expansion cohorts are commonly included to enroll more patients at the RP2D
- Endpoints
  - Toxicity
  - PK
  - Efficacy

Expansion Cohorts

- Review of phase I trials 2004-2014 published J Clin Oncol (Behtaj et al. J Clin Oncol 33, 2015 (S;abs e13585)
  - Expansion at RP2D in 40.3% of studies
  - Majority did not provide a statistical sample size for EC
  - 8.8% lead to change in MTD/RP2D
  - Expansion did not circumvent need for phase II trial
- Review of 611 single agent phase I trials identified by systematic review of MEDLINE and EMBASE after 2006 (Manji et al. J Clin Oncol; 31(33)
- Expansion cohort included in 24%, more likely if recent
  - Objectives (74%)
    - Safety 80%; Efficacy 45%; PK 28%; PD 23%; Patient enrichment 14%
  - 13% led to modification of RP2D

Expansion Cohorts

- **Potential designs include:**
  - **Fixed- sample size set to reach a certain level of precision of a DLT**
  - **Model based designs**
  - **Randomize between two cohorts**

Biomarker definition

- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacological responses to a therapeutic intervention

J Ezzelle et al. J Pharm Biomed Anal 200; 46

Biomarkers

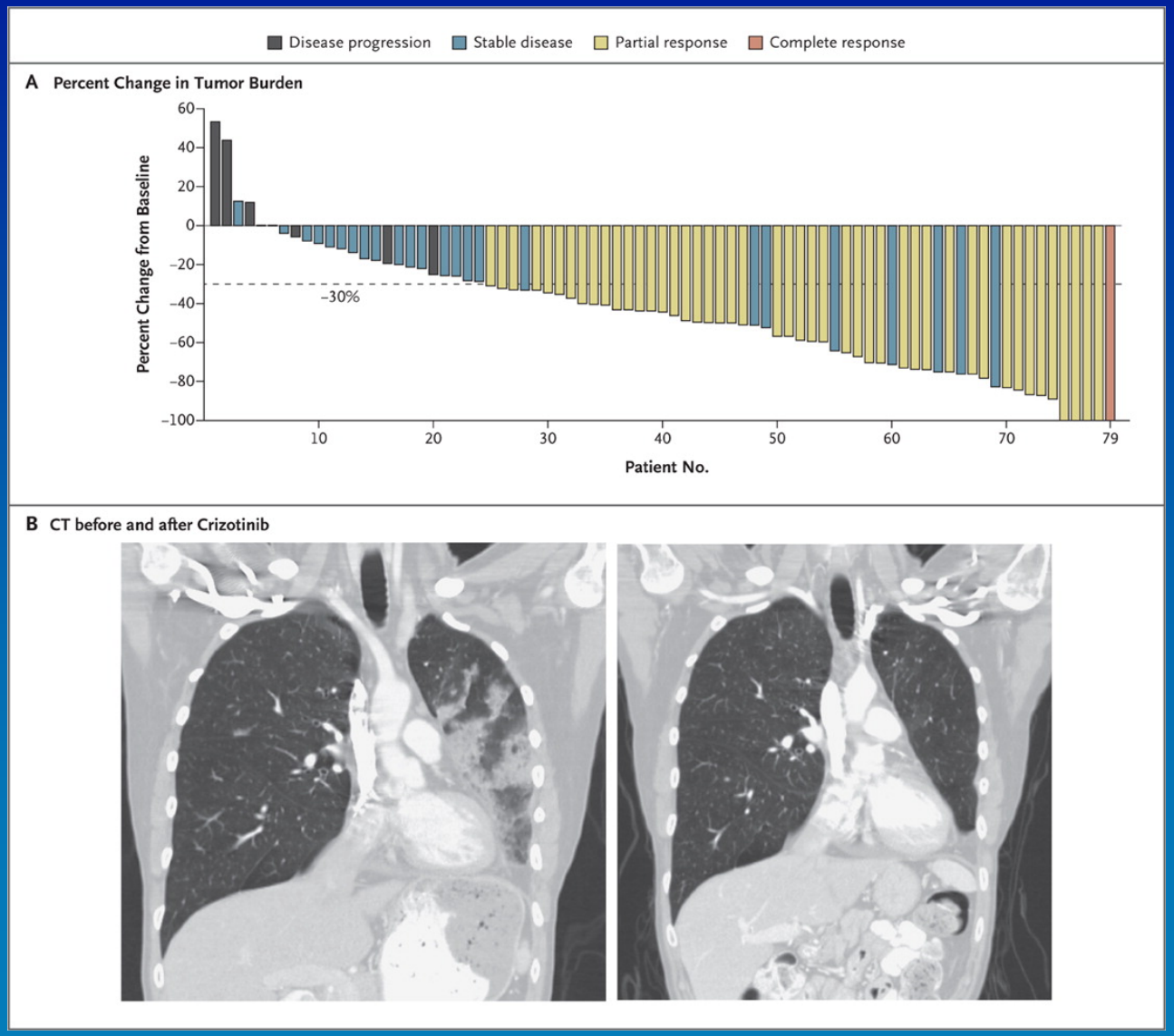
Biomarker	Role	Examples
Integral biomarker	Required for trial to proceed	Eligibility criterion Used to guide dose escalation
Integrated biomarker	Identify or validate a marker that is planned for use in future studies, testing a hypothesis	Biomarker studied at the RP2D or at selected doses to confirm effect on target
Exploratory biomarker	Trial data used to develop biomarker and or assays, or to better understand therapeutic agent potential, generating a hypothesis	Retrospective biomarker analyses Pilot or feasibility biopsies Exploratory/ hypothesis generating

J Dancey et al. Clin Cancer Research. 2010; 16

Integral Biomarkers

- **Optimal biologic dose**
  - **Cytotoxic agents - Dose response and toxicity relationship**
  - **MTA differ**
- **Optimal dose that produces a biological outcome of interest in a proportion of patients (minimum biologically active dose) or in a larger proportion of patients (optimum biologically active dose)**
- **Trials can be designed to incorporate the biomarker, escalating doses based on proportion of patients with evidence of biological effect**

Integral Biomarkers- Patient selection Response to ALK Inhibition



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Kwak EL et al. N Engl J Med 2010;363:1693-1703.

Pharmacokinetics

- Provide data on aspects including
  - Are the concentrations reached in the blood at levels that are active in pre-clinical models
  - How long is drug present
  - How is drug metabolised/ eliminated
- Some trial designs have a PK endpoint- dose escalate to a target PK
- More commonly PK data is used to guide decisions regarding route and schedule or discontinuation of development of drug

Summary

- Phase I clinical trials critical step in the evaluation of a new drug
- Patient safety is the most important consideration
- There are multiple potential phase I trial designs, but the majority of phase I trials follow traditional design with RP2D based on toxicity/MTD
- Biomarkers have the potential to enhance the development of new therapies when incorporated in early clinical trials, but careful attention to the intended role and assay etc is important