Princess Margaret Hospital
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Phase I Trials

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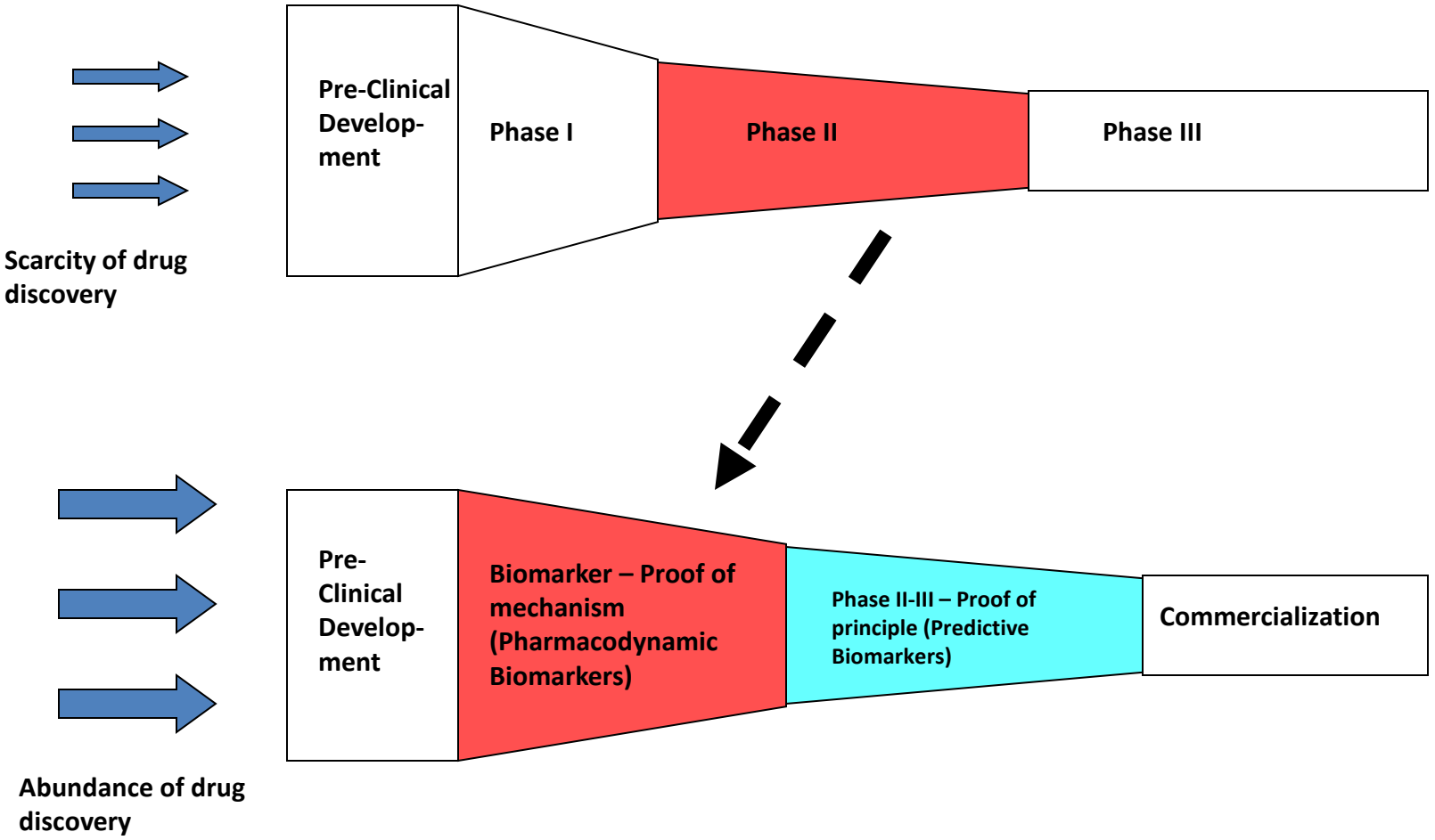
The Drug Development Paradigm



Adapted from Eli Lilly and Company

Definition(s) of a phase I trial

- **First evaluation of a new cancer therapy in humans**
  - First-in-human, first-in-kind (e.g. the first compound ever evaluated in humans against a new molecular target), single-agent
  - First-in-human, but not first-in-kind (i.e. others agents of the same class have entered human testing), single-agent

Definition(s) of a phase I trial

- **First evaluation of a new cancer therapy in humans**
  - Investigational agent + investigational agent
  - Investigational agent + approved agent(s)
  - Approved agent + approved agent(s)
  - Approved or investigational agent with pharmacokinetic focus (e.g. adding of CYP inhibitor to enhance drug levels)
  - Approved or investigational agent with pharmacodynamic focus (e.g. evaluation using functional imaging)
  - Approved or investigational agent with radiotherapy

Objectives of a phase I trial

- **Primary objective:**
  - Identify dose-limiting toxicities (DLTs) and the recommended phase II dose (RPTD)

- **Secondary objectives:**
  - Describe the toxicity profile of the new therapy in the schedule under evaluation
  - Assess pharmacokinetics (PK)
  - Assess pharmacodynamic effects (PD) in tumor and/or surrogate tissues
  - Document any preliminary evidence of objective antitumor activity

Definitions of key concepts in phase I trials

- **Dose-limiting toxicity (DLT):**
  - Toxicity that is considered unacceptable (due to severity and/or irreversibility) and limits further dose escalation
  - Specified using standardized grading criteria, e.g. Common Terminology Criteria for Adverse Event (CTCAE v3.0; v4.0 release in May 2009)
  - DLT is defined in advance prior to beginning the trial and is protocol-specific
  - Typically defined based on toxicity seen in the first cycle

Definitions of key concepts in phase I trials

- Examples of DLTs – chronic (daily) dosing:
  - Threshold for DLTs is lower
  - Some Grade 2 toxicities may be unacceptable and intolerable due to their persistence and lack of time period for recovery
  - Examples:
    - Grade 2 intolerable or worse non-hematologic toxicity despite supportive measures
    - Grade 3 or worse hematologic toxicity
    - Inability to complete a pre-specified percentage of treatment during the cycle due to toxicity (e.g. missing 10-15% of doses)

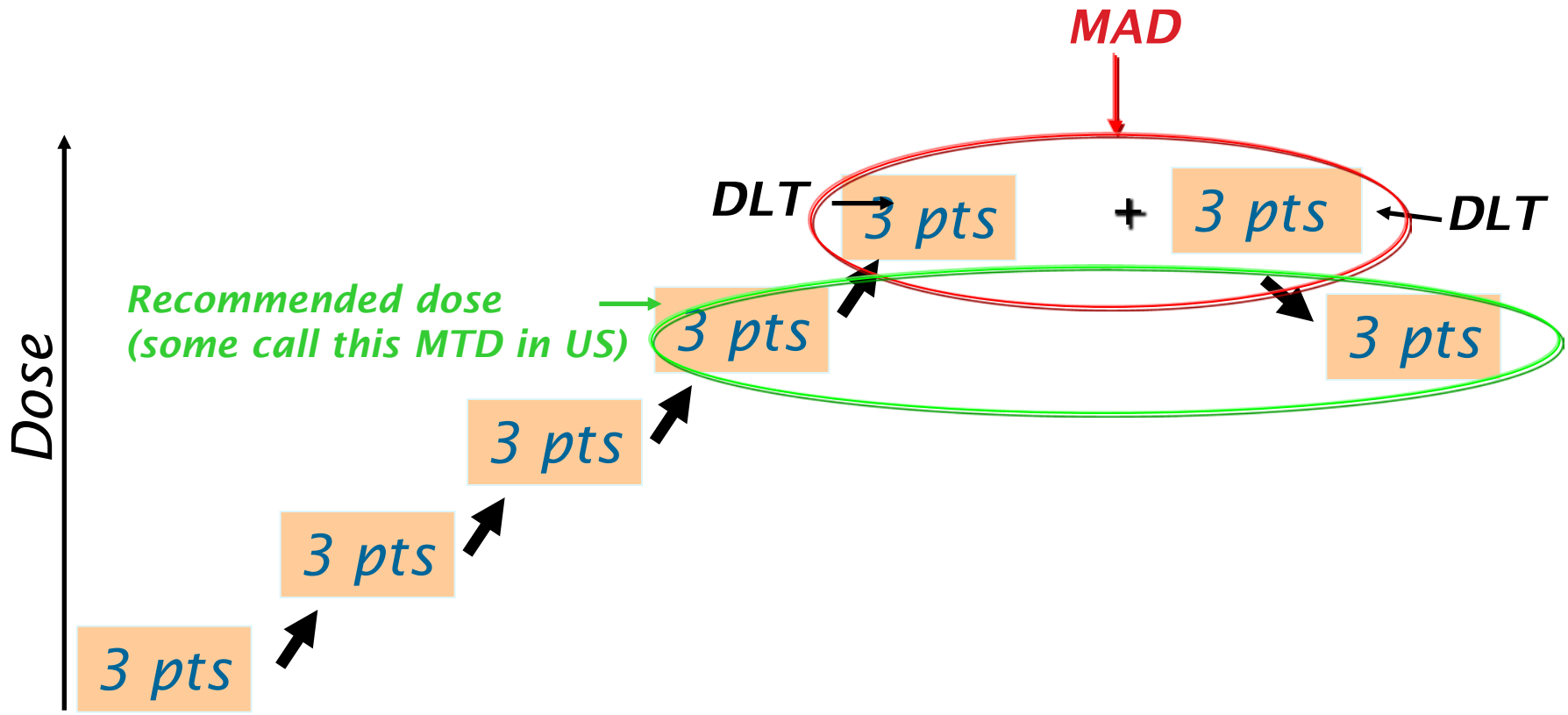
Definitions of key concepts in phase I trials

- Examples of DLTs – intermittent dosing:
  - Generally can tolerate higher degrees of toxicity because the interval between treatments allows for rest and recovery
  - Examples:
    - Grade 3 or worse non-hematologic toxicity despite supportive measures
    - ANC $< 0.5 \times 10^9$/L for $\geq$ 5 or 7 days
    - Febrile neutropenia (ANC $< 1 \times 10^9$/L, fever $\geq 38.5°C$)
    - Platelets $< 25 \times 10^9$/L or thrombocytopenic bleeding
    - Inability to re-treat patient within 2 weeks of scheduled treatment

Definitions of key concepts in phase I trials

- **Maximum administered dose (MAD), maximum tolerated dose: confusing**
- **More important term: Recommended phase II dose (RPTD or RD):**
  - Dose associated with DLT in a pre-specified proportion of patients (e.g. < 33%) – dose that will be used in subsequent phase II trials

Phase I trial design: standard 3+3 design



Adapted from E. Eisenhauer

Definitions of key concepts in phase I trials

- Optimal biological dose (OBD):
  - Dose associated with a pre-specified desired effect on a biomarker
  - Examples:
    - Dose at which $\geq$ XX% of patients have inhibition of a key target in tumor/surrogate tissues
    - Dose at which $\geq$ XX% of patients achieve a pre-specified immunologic parameter
  - Challenge with defining OBD is that the "desired effect on a biomarker" is generally not known or validated before initiation of the phase I trial

Definitions of key concepts in phase I trials

- Pharmacokinetics (PK):
  - "what the body does to the drug"
  - absorption, distribution, metabolism and excretion
  - PK parameters: Cmax, AUC (drug exposure), t1/2, Clearance, etc.

- Pharmacodynamics (PD):
  - "what the drug does to the body"
  - e.g. nadir counts, non-hematologic toxicity, molecular correlates, imaging endpoints

Phase I trials: fundamental questions

- At what dose do you start?
- What type of patients?
- How many patients per cohort?
- How quickly do you escalate?
- What are the endpoints?

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Preclinical toxicology

- Typically a rodent (mouse or rat) and non-rodent (dog or non-human primate) species

- Reality of animal organ specific toxicities – very few predict for human toxicity
  - Myelosuppression and gastrointestinal toxicity more predictable
  - Hepatic and renal toxicities – large false positive

- Toxicologic parameters:
  - LD10 – lethal dose in 10% of animals
  - TDL (toxic dose low) – lowest dose that causes any toxicity in animals
  - NOAEL – no observed adverse effect level

Phase I trials: starting dose

- 1/10 of the LD10 in rodents

or

(depending on sensitivity of the species)

- 1/6 or 1/3 of the TDL in large animals

- Unless preclinical studies suggest a very steep dose/toxicity curve

Conversion of animal dose to human equivalent doses (HED)

Species	To convert animal dose in mg/kg to dose in mg/m^2, multiply by Km below:	To convert animal dose in mg/kg to HED in mg/kg, either:	
		Divide animal dose by	Multiple animal dose by
Human	37	–	–
Child (20 kg)	25	–	–
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

Phase I trials: fundamental questions

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Phase I patient population

- "Conventional" eligibility criteria- examples:
  - Advanced solid tumors unresponsive to standard therapies or for which there is no known effective treatment
  - Performance status (e.g. ECOG 0 or 1)
  - Adequate organ functions (e.g. ANC, platelets, Creatinine, AST/ALT, bilirubin)
  - Specification about prior therapy allowed
  - Specification about time interval between prior therapy and initiation of study treatment
  - No serious uncontrolled medical disorder or active infection

Phase I patient population

- "Agent-specific" eligibility criteria – examples:
  - Restriction to certain patient populations – must have strong scientific rationale
  - Specific organ functions:
    - For example – cardiac function restrictions (e.g. QTc $\leq$ 450-470 ms, LVEF $\geq$ 45%, etc) if preclinical data or prior clinical data of similar agents suggest cardiac risks
    - For example – no recent (6-12 months) history of acute MI/unstable angina, cerebrovascular events, venous thromboembolism; no uncontrolled hypertension; no significant proteinuria, for antiangiogenic agents
  - Prohibited medications if significant risk of interaction with study drug

Phase I trials: fundamental questions

- At what dose do you start?
- What type of patients?
- How many patients per cohort?
- How quickly do you escalate?
- What are the endpoints?

Cohort dose escalation: standard 3+3 design

# of pts with DLT	Action
0/3	Increase to next level
1/3	Accrue 3 more pts at same dose level
1/3 + 0/3	Increase to next dose level
1/3 + 1/3	Stop: recommend previous dose level
1/3 + 2/3	Stop: recommend previous dose level
1/3 + 3/3	Stop: recommend previous dose level
2/3	Stop: recommend previous dose level
3/3	Stop: recommend previous dose level

Many phase I trials accrue additional patients at the RPTD to obtain more safety, PK, PD data (but this expansion cohort does not equal to a phase II trial)

Phase I trials: fundamental questions

- At what dose do you start?
- What type of patients?
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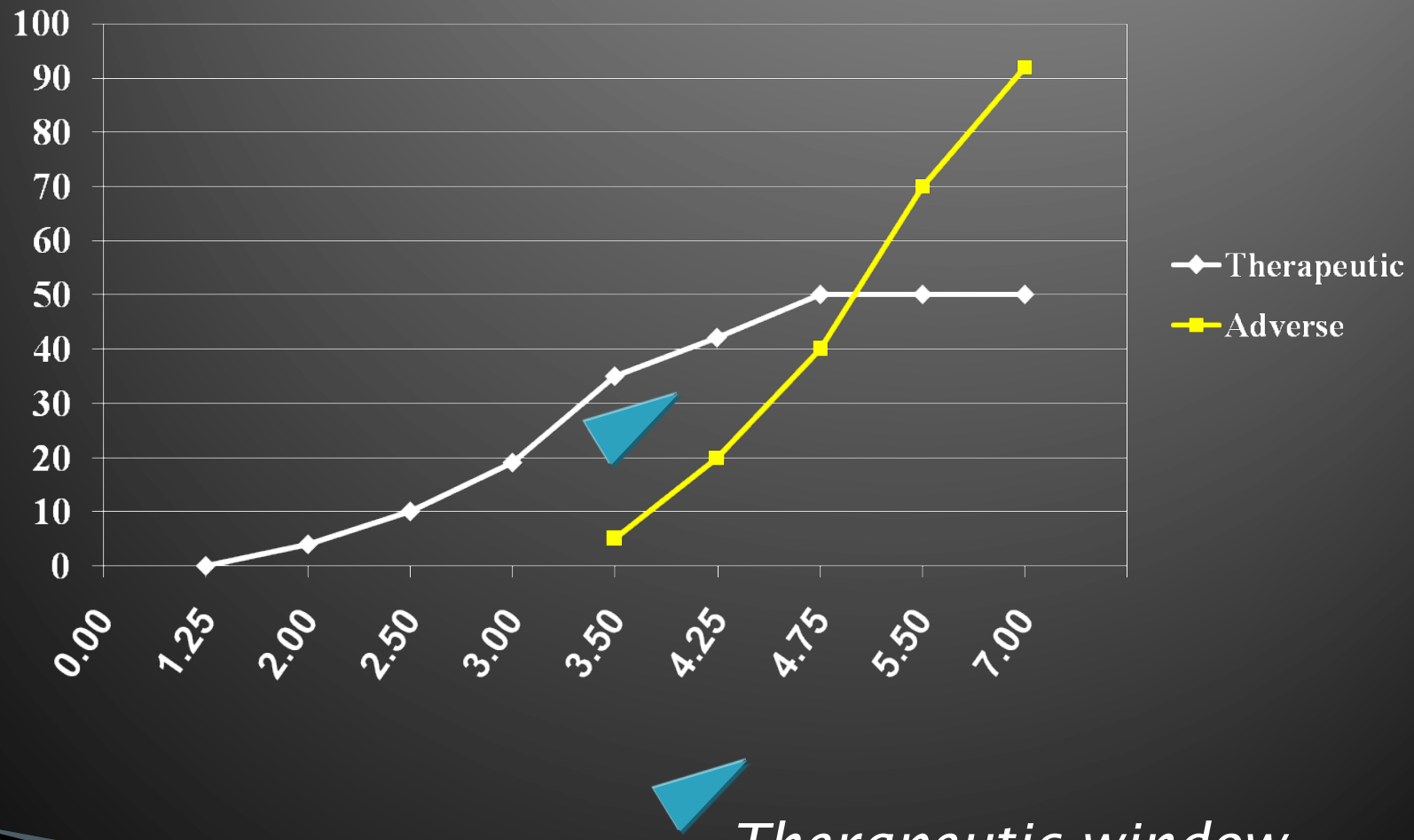
Phase I trial basic principles

- Start with a safe starting dose
- Minimize the number of pts treated at sub-toxic (and thus maybe sub-therapeutic) doses
- Escalate dose rapidly in the absence of toxicity
- Escalate dose slowly in the presence of toxicity

Phase I trial assumption

- The higher the dose, the greater the likelihood of efficacy
  - Dose-related acute toxicity is regarded as a surrogate for efficacy
  - The highest safe dose is the dose most likely to be efficacious
  - This dose-effect assumption is primarily for cytotoxic agents and may not apply to molecularly targeted agents

Dose-response: efficacy and toxicity



P1T Designs for Targeted Agents (till 2003)

Reasons for halting dose escalation, targeted agents given as single-agents

Reason	*-2003*	*2007-2008*
Toxicity	*36 (60%)*	*20 (63%)*
PK (+/- other)	*8 (13%)*	*4 (13%)*
Others		
Design, maximum planned dose	*5*	
Limited drug Supply	*4*	
Other phase I results	*2*	
Drug activity observed	*1*	
Not stated	*4*	
Total	*60*	*32*

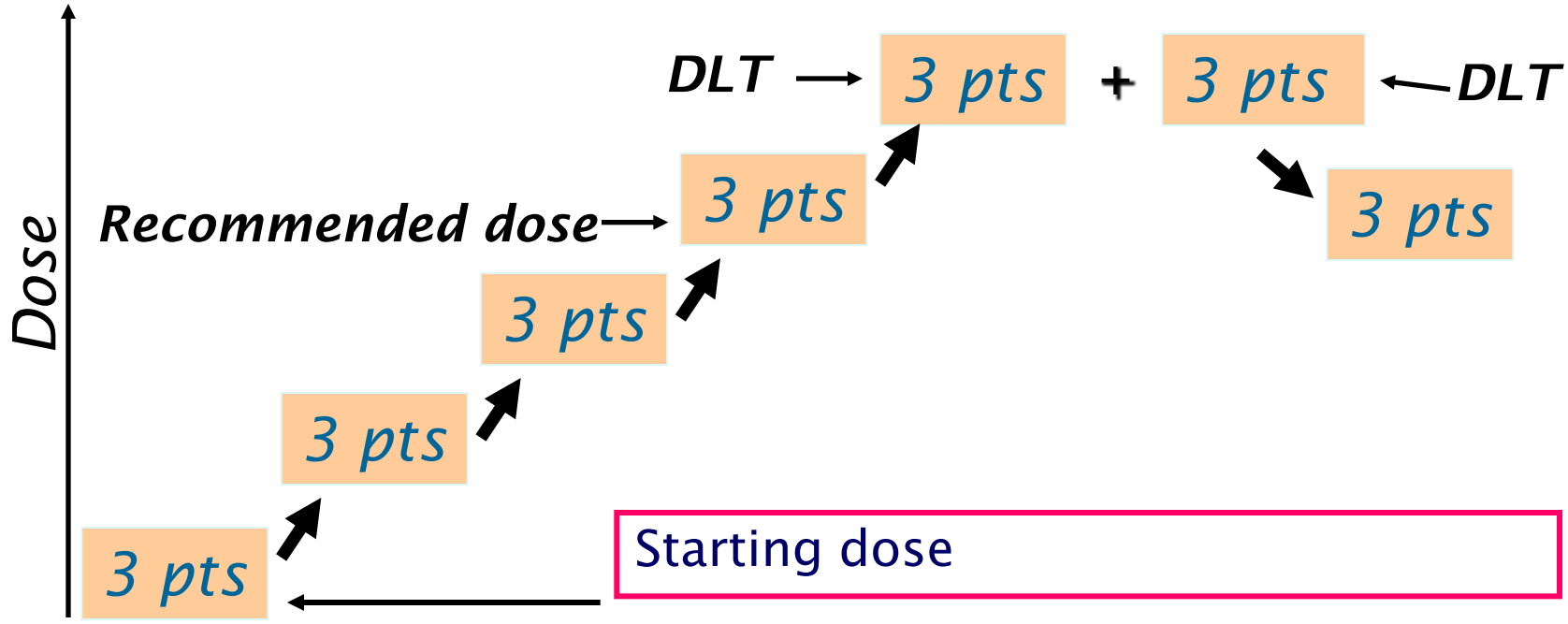
Parulekar and Eisehauer, JNCI, 2004

Le Tournea, Lee, Siu, JNCI, 2009

Phase I Trial Design :
Modified Fibonacci Dose Escalation (Rule-based)

- Attributed to a merchant from the 13th century
- Doses increase by: 100%, 66%, 50%, 40%, 33%, etc.
- Standard "3+3" design: 3 patients per cohort, escalating to 6 if DLT occurs
- Dose escalate until DLT observed and MTD/RPTD defined
- Advantages:
  - relatively safe, straightforward, clinician-friendly
- Disadvantages:
  - lacks statistical foundation and precision, potentially treating a large proportion of patients at sub-therapeutic doses, time consuming

Phase I trial design: standard 3+3 design

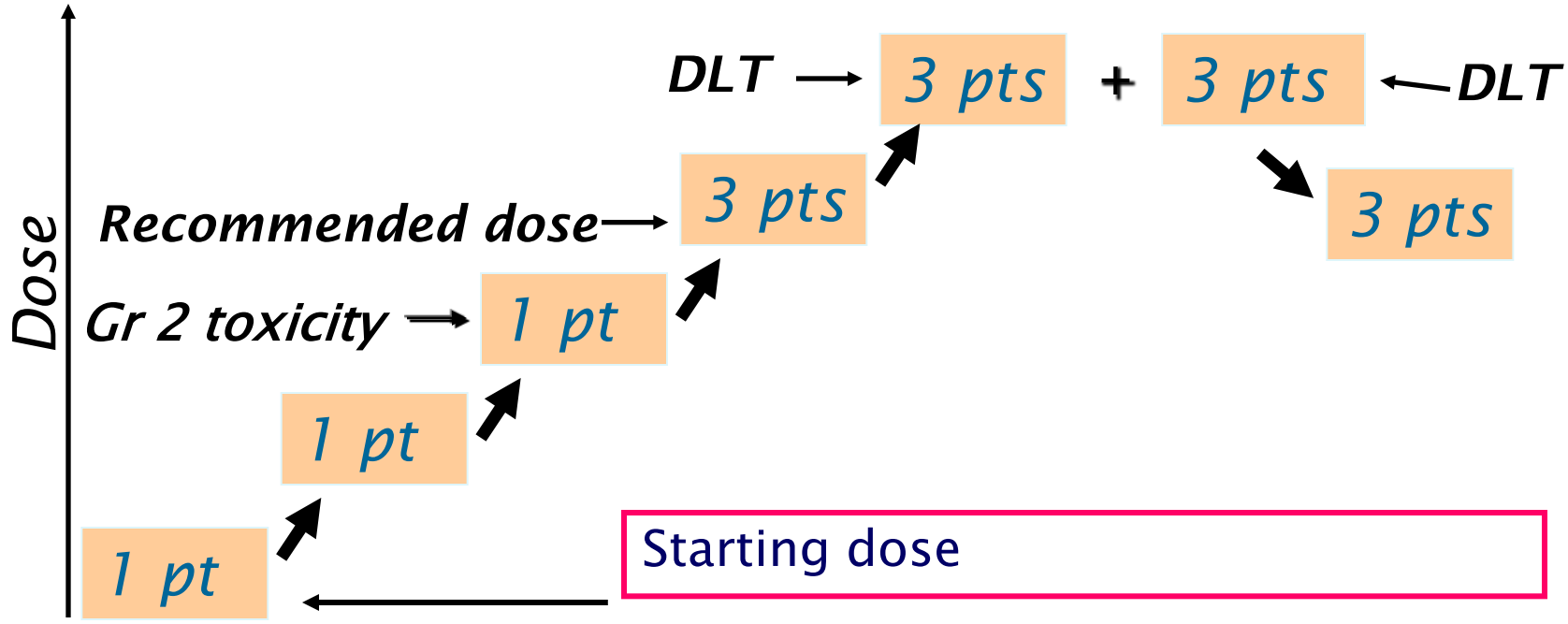


Eisenhauer et al.

Phase I Trial Design:
Accelerated Titration Design (Rule-based)

- First proposed by Simon et al (J Natl Cancer Inst 1997)
- Several variations exist:
  - usual is doubling dose in single-patient cohorts till Grade 2 toxicity
  - then revert to standard 3+3 design using a 40% dose escalation
  - intrapatient dose escalation allowed in some variations
- More rapid initial escalation

Phase I trial design: accelerated titration



Phase I Trial Design:
Modified Continual Reassessment Method (MCRM; Model-based)

- Bayesian method
- Pre-study probabilities based on preclinical or clinical data of similar agents
- At each dose level, add clinical data to better estimate the probability of MTD being reached
- Fixed dose levels, so that increments of escalation are still conservative

Phase I Trial Design: *Modified Continual Reassessment Method (MCRM; Model-based)*

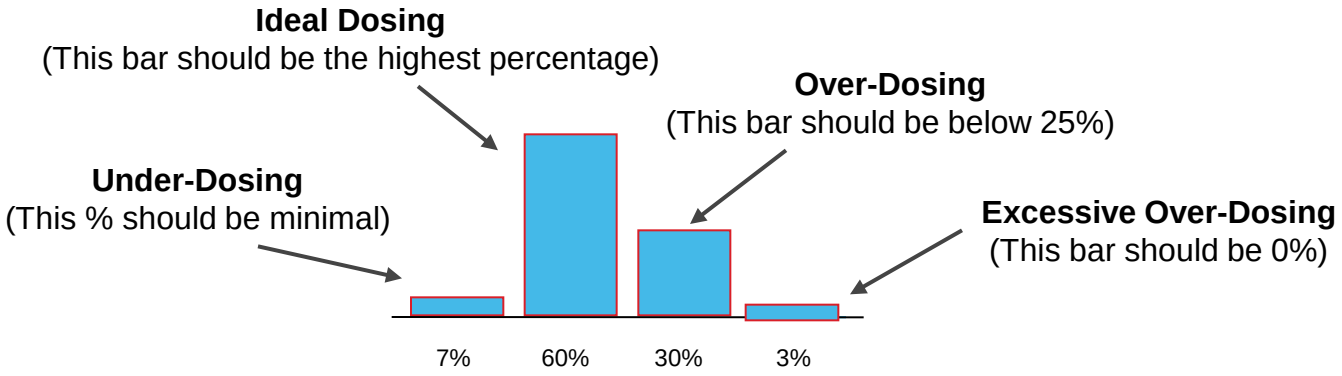
- Example: Pre-set dose levels of 10, 20, 40, 80, 160, 250, 400
- If after each dose level, the statistical model predicts a MTD higher than the next pre-set dose level, then dose escalation is allowed to the next pre-set dose level
- Advantages:
  - Allows more dose levels to be evaluated with a smaller number of patients
  - More patients treated at or closer to "therapeutic" dose
- Disadvantages:
  - Does not save time, not easily implemented if without access to biostatistician support

Phase I Trial Design:
Dose Escalation with Overdose Control (EWOC; Model-based)

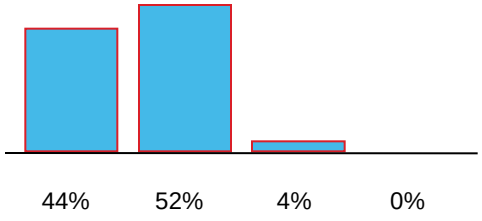
- Bayesian method
- After each cohort of patients, the posterior distribution is updated with DLT data to obtain π_d (probability of DLT at dose d). The recommended dose is the one with the highest posterior probability of DLT in the "ideal dosing" category
- The overdose control mandates that any dose that has > 25% chance of being in the "over-dosing" or "excessive over-dosing" categories, or > 5% chance of being in the "excess-overdosing" category, is not considered for dosing

Estimated MTD Based on Bayesian Logistic Method (2-parameter evaluation with over-dose control)

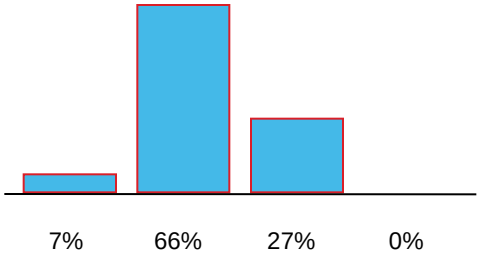
EXAMPLE of Probability of DLTs (Bayesian design)



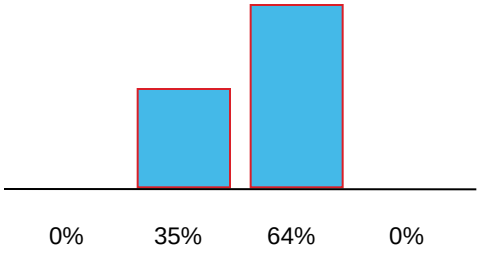
Drug at 0.5mg



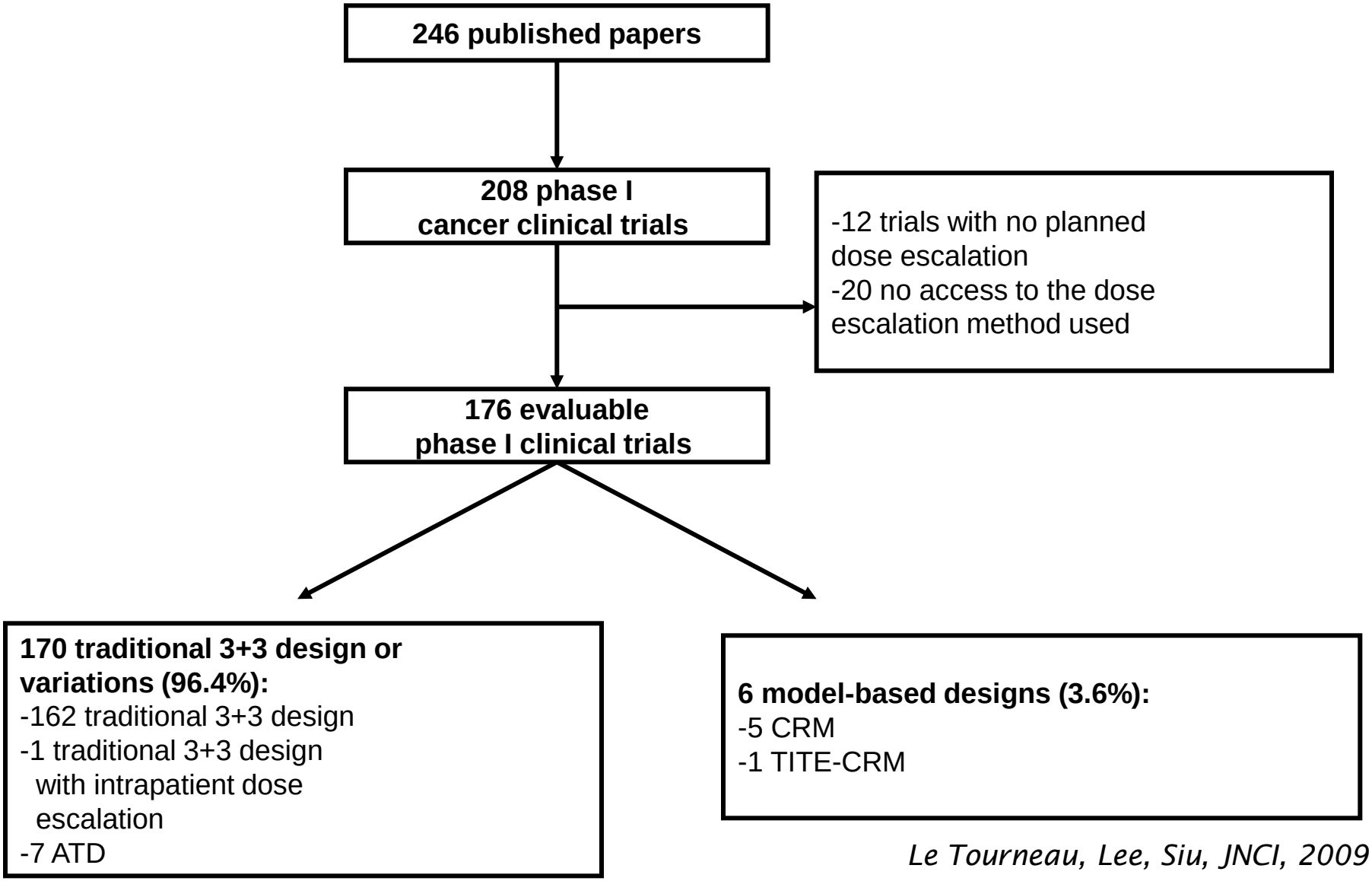
Drug at 0.75 mg



Drug at 1.0 mg



Phase I Trials 2007–8: use of new designs



Le Tourneau, Lee, Siu, JNCI, 2009

Phase I trials: fundamental questions

- At what dose do you start?
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Endpoints in phase I trials

- DLT and other toxicity – safety and tolerability
- Pharmacokinetics
- Pharmacodynamics – biological correlates, imaging endpoints
- Preliminary antitumor activity

Response Rates and Deaths from Toxic Events in Phase I Oncology Trials Involving the First Use of Agent in Humans (Horstman et al, NEJM 352, 2005)

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate* %	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events no. %
Total First use of an agent in humans	117	3164	4.8	3498	9 (0.26)
Cytotoxic chemotherapy First use of an agent in humans	43	1298	5.0	1422	7 (0.49)
Immunomodulator First use of an agent in humans	16	404	7.4	431	1 (0.23)
Receptor or signal transduction First use of an agent in humans	27	742	3.8	853	1 (0.12)
Antiangiogenesis First use of an agent in humans	8	200	7.0	228	0
Gene transfer First use of an agent in humans	0	0	0	0	0
Vaccine First use of an agent in humans	23	520	3.1	564	0

Pitfalls of phase I trials

- Chronic and late toxicities usually cannot be assessed (Postel-Vinay et al, J Clin Oncol 2011)
- Cumulative toxicities usually cannot be identified
- Uncommon toxicities will be missed

Phase I trials and infrequent toxicities

Number of patients	Probability of NOT observing a serious toxicity occuring at a rate of: 10%	20%
1	0.90	0.80
2	0.81	0.64
3	0.73	0.51
6	0.53	0.26
10	0.35	0.11
15	0.21	0.04

Probability of overlooking a toxicity:
$P_{OT}(p) = (1-p)^n$; n = sample size, p = true toxicity rate

The successful phase I team

- Scientists
- Fellows
- Trial nurses
- Data coordinators
- Investigators
- Lab personnel: reference, PK, PD
- Pharmacists
- Biostatisticians
- Radiologists