Phase I Trials

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Learning Objectives

- Understand the purpose of phase I trials
- Become familiar with concepts of dose limiting toxicities (DLTs), recommended phase II dose (RPTD), and optimal biological dose (OBD)
- Provide an overview of the types of trial designs used determine the RPTD
- Introduction to the role of biomarkers in phase I trials

Definitions of Phase I Trial

First evaluation of a new cancer therapy in humans

- First-in-human, first-in-class single agent
- First-in-human, non first-in-class single agent
- Combination of novel agents
- Combination novel agent and approved agent
- Combination of approved agents
- Combination of novel agent and radiation therapy

Eligible patients usually have refractory solid tumors of any type

Prerequisites for Phase I

- Unmet clinical need
- Biological plausibility (target validation)
- Expectation of benefit (preclinical activity)
- Reasonable expectation of safety (preclinical toxicology)
- Basis for selection of starting dose

Objectives of 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 anti-tumor activity

Key Concepts: DLT

- 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)
  - DLT is defined in advance prior to beginning the trial and is protocol-specific
  - Typically defined based on toxicity seen in the first cycle

CTCAE Criteria

- Grade 1 = MILD
- Grade 2 = MODERATE
- Grade 3 = SEVERE
- Grade 4 = LIFE-THREATENING
- Grade 5 = FATAL

DLT Definitions – 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

DLT Definitions – 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
  - Recurrent Grade 2 intolerable toxicity after interruption
  - Grade 3 or worse hematologic toxicity
  - Inability to complete a pre-specified percentage of treatment during the cycle due to toxicity (e.g. missing 20-25% of doses)

Terminology

- Terms maximum administered dose (MAD), maximum tolerated dose (MTD) are confusing

- Better Term = Recommended phase II dose (RPTD):
  - Dose associated with DLT in a pre-specified proportion of patients (e.g. < 33%) – dose that will be used in subsequent phase II trials

Key Principles of Phase I Trials

- Start with a safe starting dose
- Minimize # of pts treated at sub-toxic doses
- Escalate dose rapidly in the absence of toxicity
- Escalate dose slowly in the presence of toxicity
- Expand patient cohort at RPTD

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

Patient Population

- **"Agent-specific" eligibility criteria- examples:**
  - Specific organ exclusions:
    - Cardiac function (e.g. QTc ≥450-470 ms, LVEF ≤ 50%, etc), acute MI/CVA if preclinical data or prior clinical data of similar agents suggest cardiac risks
    - Recent hemorrhage or ongoing anticoagulation for agents with bleeding risk (ie. antiangiogenic)
    - Diabetes or fasting plasma hypergylcemia ≥ 7.9 mmol/L for agents with risk of hyperglycemia (ie. PI3K/mTOR, IGF-1R)
  - Prohibited medications if significant risk of interaction with study drug
  - Prior exposure to drug in same class

Pre-clinical 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

- Typical starting dose:
  - 1/10th of LD10 rodents = lethal dose in 10% of animal

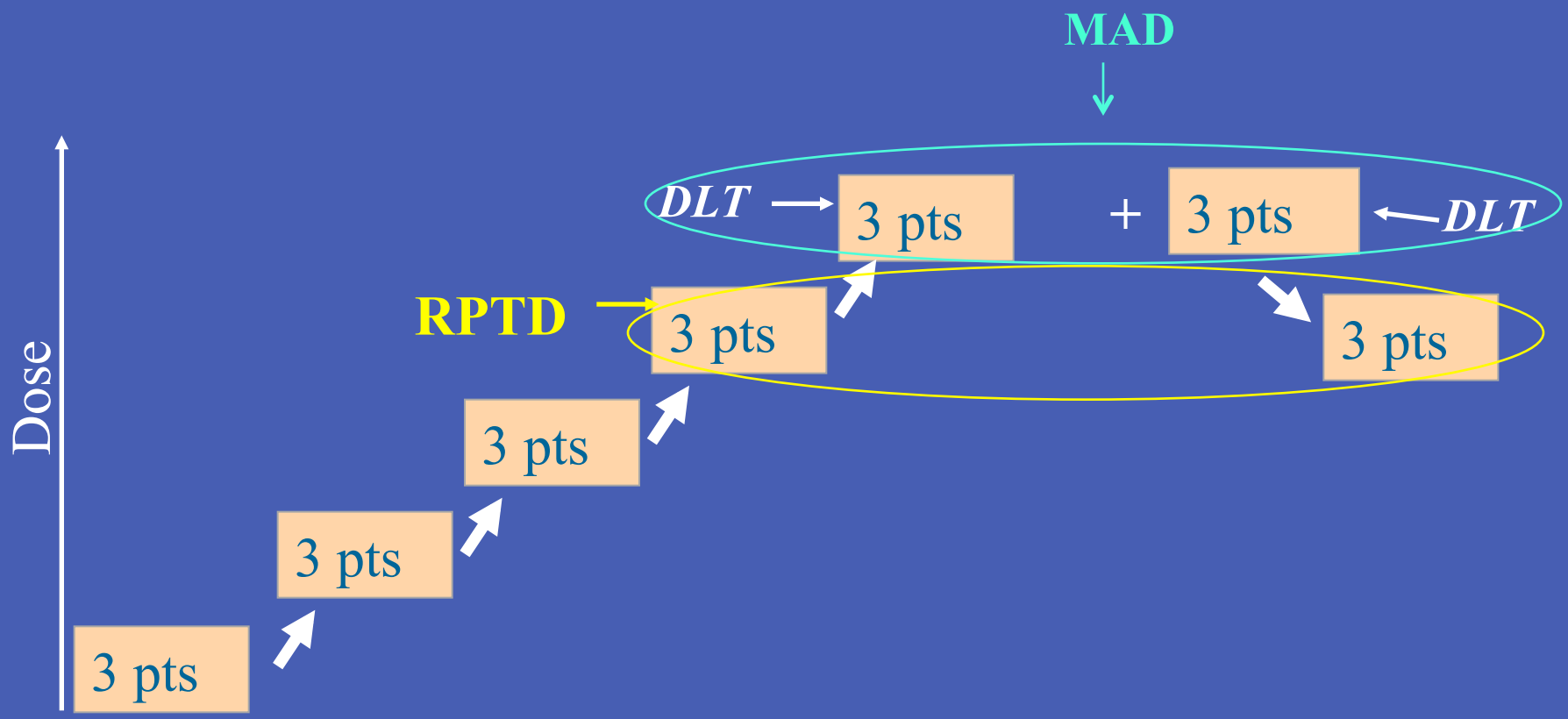
  OR
  - 1/3rd of TDL large animals = lowest dose that causes any toxicity in animals

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

Principles of Dose Escalation

- 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

Classical 3+3 Design



Typically intrapatient dose escalation is not allowed

Classical 3+3 Design

# of pts w/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

Modified Fibonacci Dose Escalation

- 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

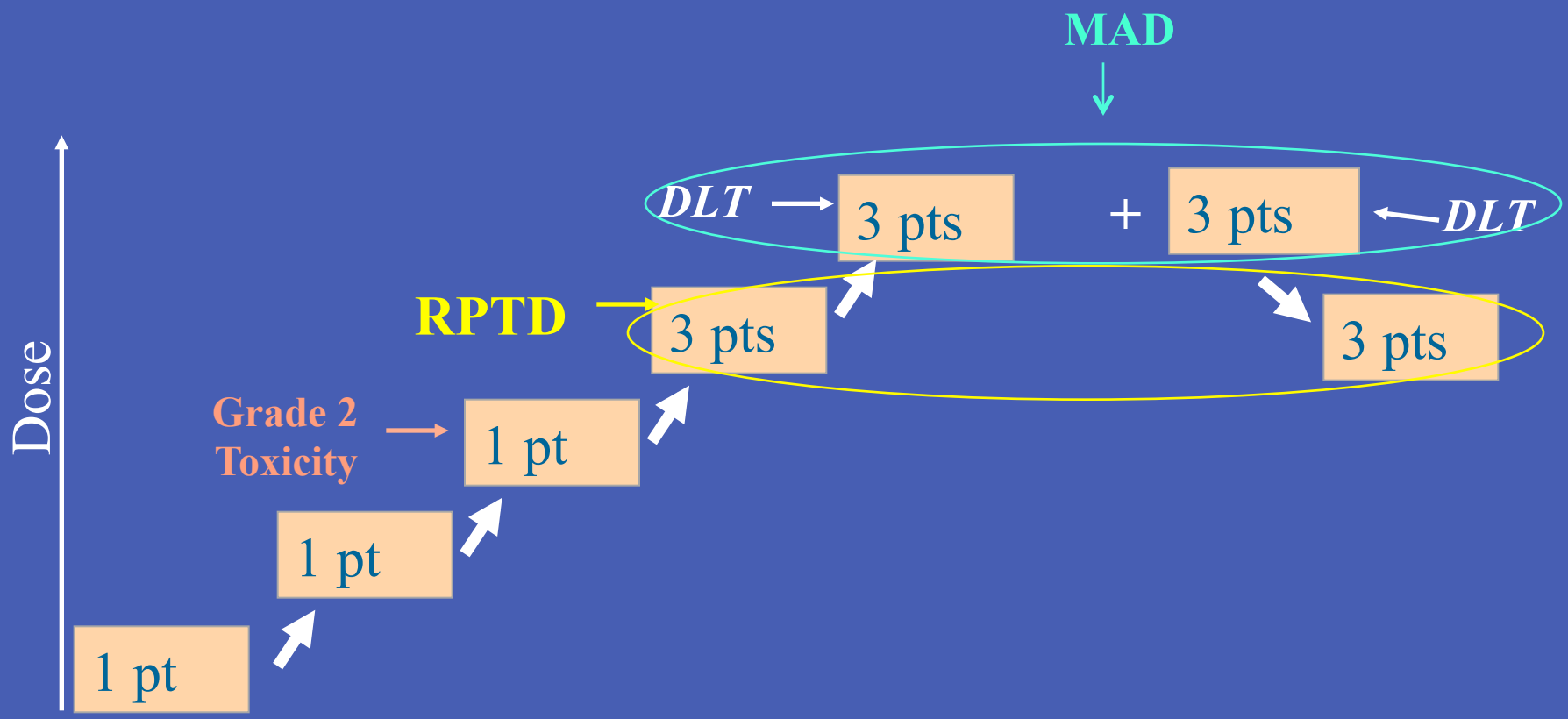
Limitations of 3+3 Design

- Many patients treated at ineffective doses in initial cohorts
- Escalation to RPTD can take a long time
- High risk of severe toxicity in late cohorts
- Wide confidence intervals for RPTD

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

Classical 3+3 Design



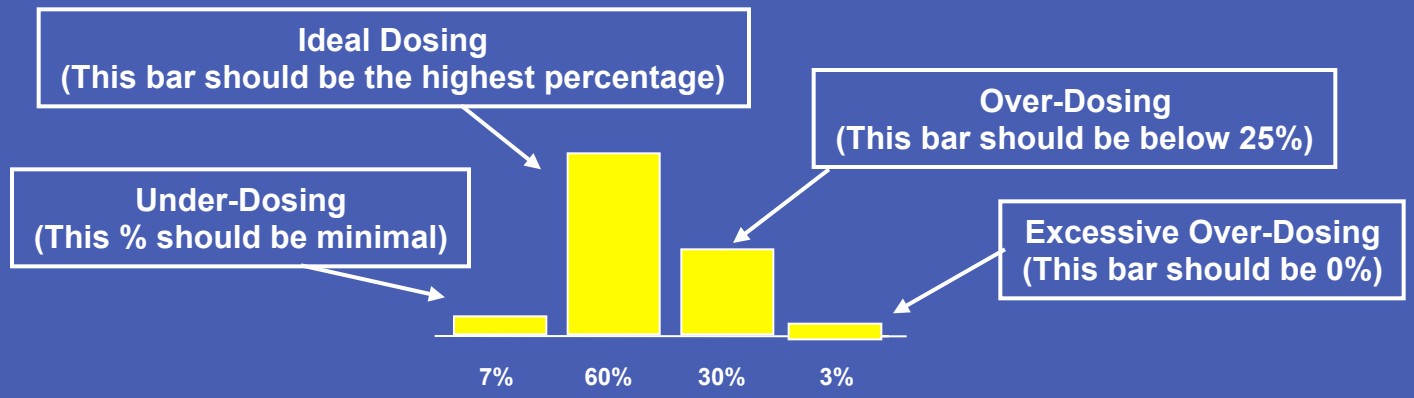
Modified Continual Reassessment Method (mCRM)

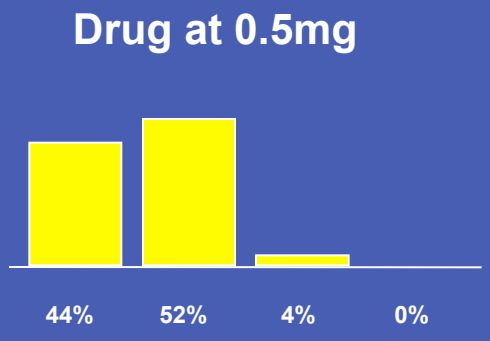
- Bayesian method
- Pre-study probabilities based on preclinical or clinical data of similar agents
- At each dose level, add clinical data to better estimate the probability of RPTD being reached
- Fixed dose levels for escalation
- Advantages – more pts treated at therapeutic levels, more dose levels explored
- Disadvantages – requires biostatistician, does not save time

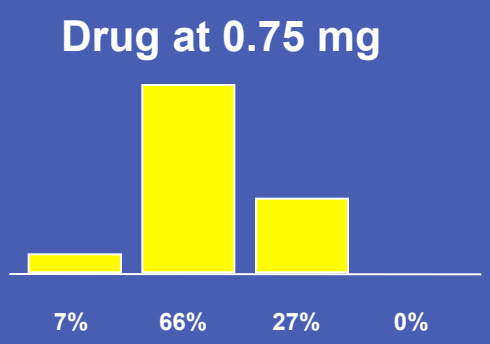
Dose Escalation with Overdose Control (EWOC)

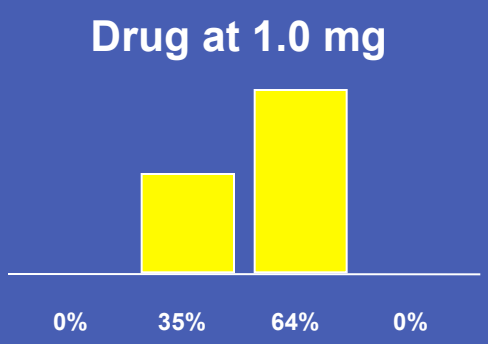
- Bayesian method
- After each cohort of patients, the posterior distribution is updated with DLT data to obtain πd (probability of DLT at dose d). The recommended dose is the one with the highest posterior probability of DLT in the "ideal dosing" category
- The overdose control mandates that any dose 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

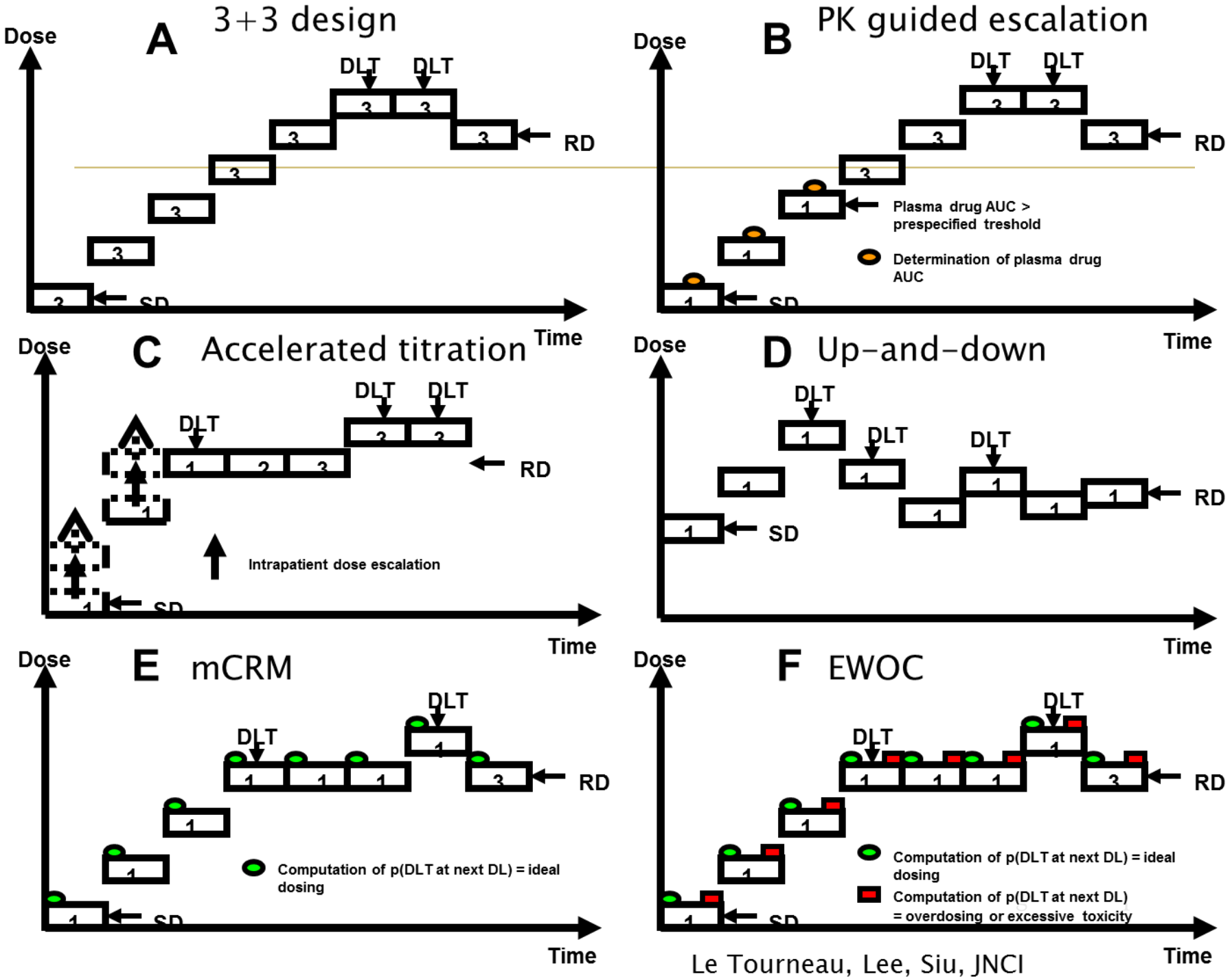
Example of EWOC Design







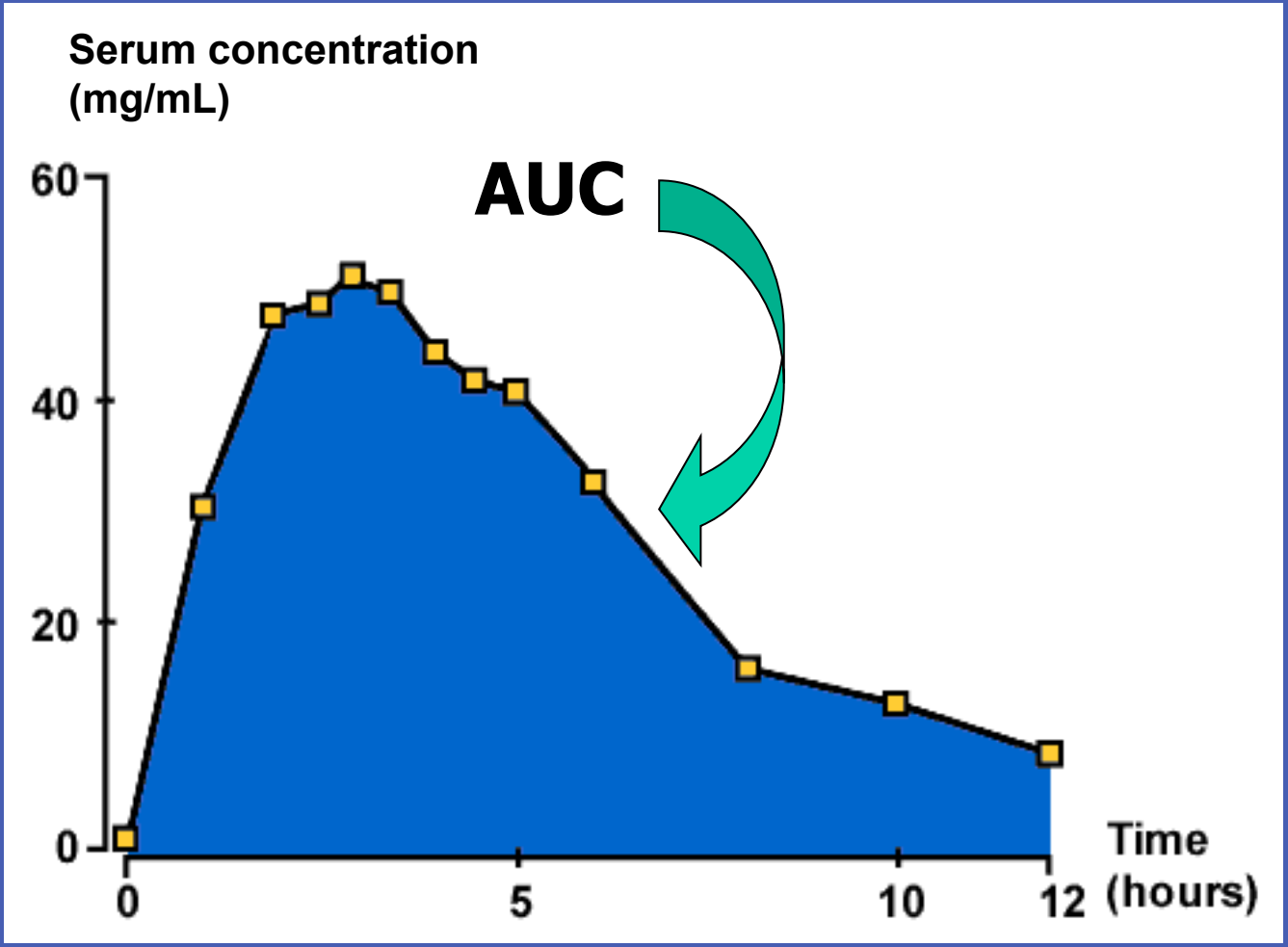



A 3+3 design
Dose
DLT
DLT
RD
SD
Time
B PK guided escalation
Dose
DLT
DLT
RD
Plasma drug AUC > prespecified treshold
Determination of plasma drug AUC
SD
Time
C Accelerated titration
Dose
DLT
DLT
DLT
RD
Intrapatient dose escalation
SD
Time
D Up-and-down
Dose
DLT
DLT
DLT
RD
SD
Time
E mCRM
Dose
DLT
DLT
RD
Computation of p(DLT at next DL) = ideal dosing
SD
Time
F EWOC
Dose
DLT
DLT
RD
Computation of p(DLT at next DL) = ideal dosing
Computation of p(DLT at next DL) = overdosing or excessive toxicity
SD
Time
Le Tourneau, Lee, Siu, JNCI

Pharmacokinetic (PK) Assessment

- "What the body does to the drug"
  - Absorption, distribution, metabolism, and excretion
- PK parameters – provide information about the drug and/or its metabolites
  - Cmax (peak concentration)
  - AUC (exposure)
  - $T_{1/2}$ (half-life)
  - Clearance (elimination)
- Requires serial sampling to characterize fully
  - ie. Pre-dose, 30m, 1h, 2h, 4h, 6h, 8h, 24h
  - Cycle 1 Day 1 and repeat when drug is expected to have reached steady state serum concentrations

PK: Time x Concentration Plot



Challenges of Molecularly Targeted Agents (MTAs)

- General requirement for long-term administration: *pharmacology and formulation critical*
- Difficulty in determining the optimal dose in phase I: *MTD versus Optimal Biological Dose (OBD)*
- Absent or low-level tumor regression as single agents: *problematic for making go no-go decisions*
- Need for large randomized trials to definitively assess clinical benefit: *need to maximize chance of success in phase III*

Key Concepts

- 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

Definition of a Biomarker

- "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"
  - » NIH Working Group, 2011

- "A molecular, cellular, tissue, or process-based alteration that provides indication of current, or more importantly, future behavior of a cancer."
  - » Hayes et al JNCI, 1996

Biomarkers in Phase I Trials

- Based on pre-clinical studies
  - Pharmacokinetics
  - Proof-of-mechanism
  - Establish optimal biological dose in some trials (especially if little or no toxicity expected)
  - Molecular enrichment
    - ✓ Proof-of-concept – anti-tumor activity

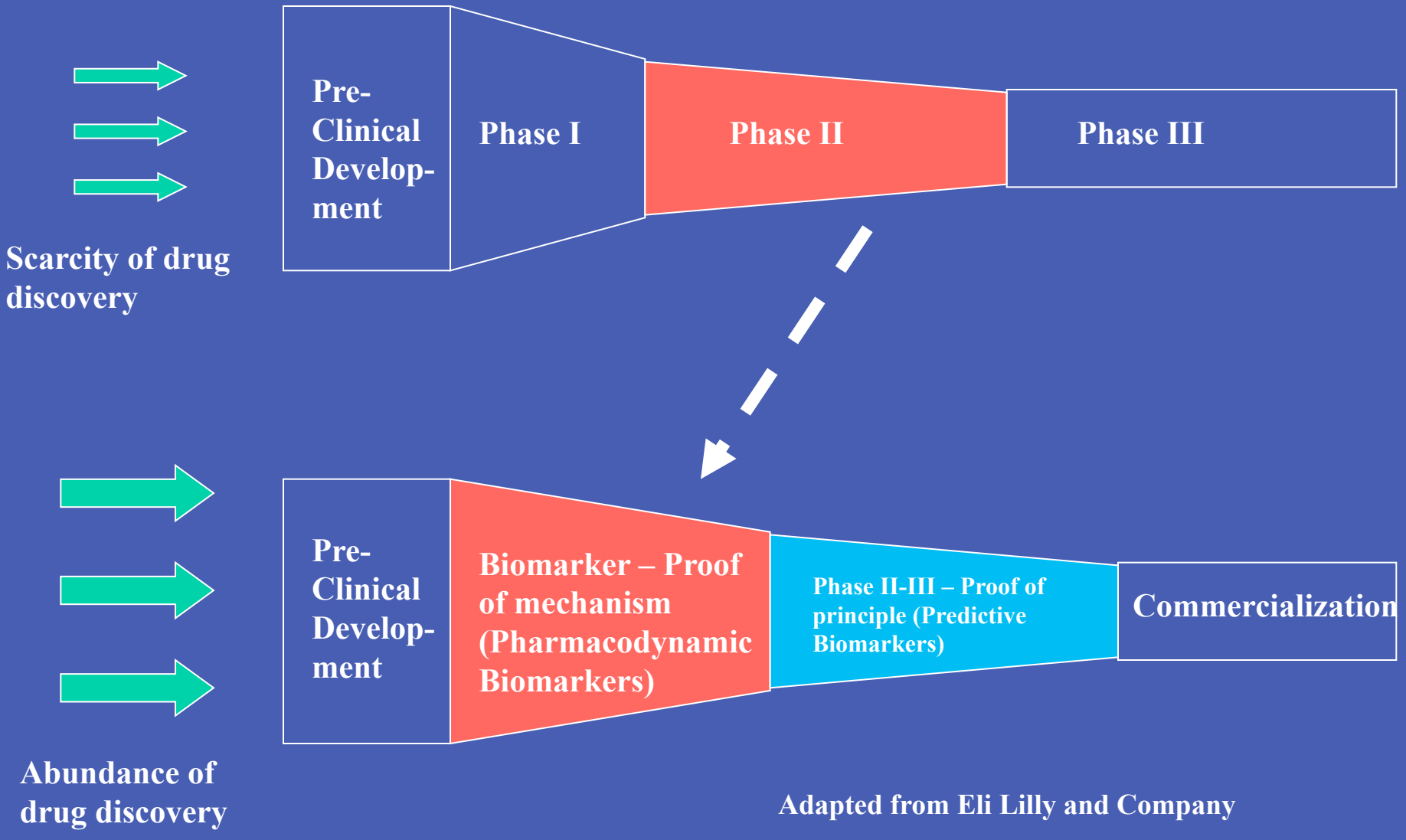
Pharmacodynamic Biomarkers (PD)

- "What the drug does to the body (or tumor)"
  - Provide therapeutic information about the effect of a therapeutic intervention on the patient and/or tumor
- Tumor PD biomarkers
  - Phosphoprotein (IHC)
  - Gene expression (RT-PCR, microarray)
  - Cell surface markers (Flow cytometry)
  - Functional imaging
    - FDG-PET, FLT-PET, DCE MRI, etc
- Surrogate Normal Tissue PD biomarkers
  - Hair follicles
  - Skin biopsies
  - Peripheral blood mononuclear cells (PBMCs)

Pharmacodynamic Endpoints

- Phase I PD biomarkers
  - Requires assessment before and during treatment
  - Should be correlated with PK parameters
  - Proof of mechanism
    - Is a new drug hitting its target?
  - Establish optimal biological dose
    - Especially if little of no toxicity expected (monoclonal antibodies)
  - Often more practical to perform in expansion cohort at recommended phase II dose

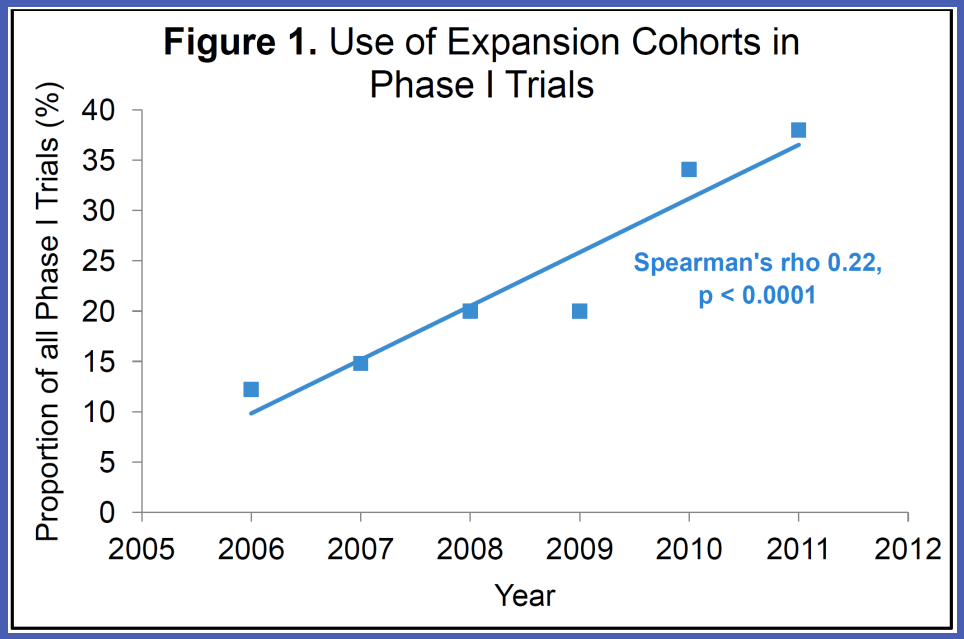
Changing Paradigm of Biomarker-Guided Early Drug Development



Adapted from Eli Lilly and Company

Expansion Cohorts in Phase I Trials

- Limited # of pts (N=6-12) treated at MTD after dose escalation
- Confirm safety and tolerability of MTD = RPTD
- Increasing use over time
- Expansion cohort ≠ properly conducted phase II

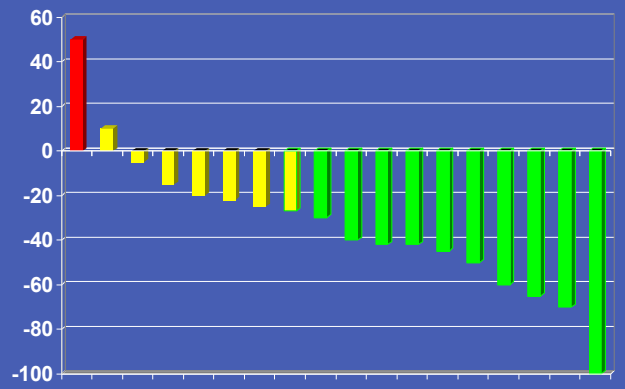


Manji A et al JCO 2013 (in press)

Enrichment Strategies for Phase I

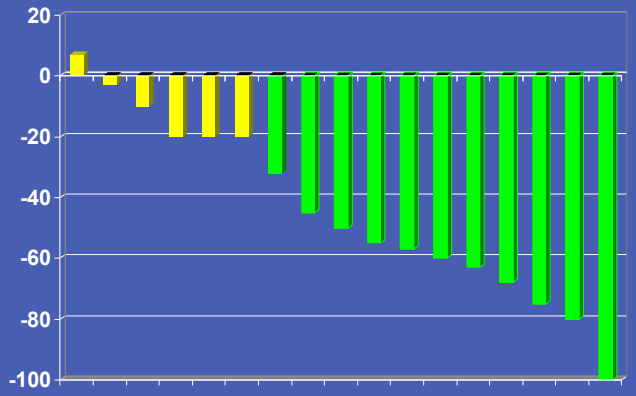
- Early testing of a new drug in enriched population can accelerate development of new drug

Crizotinib (ALK inhibitor)



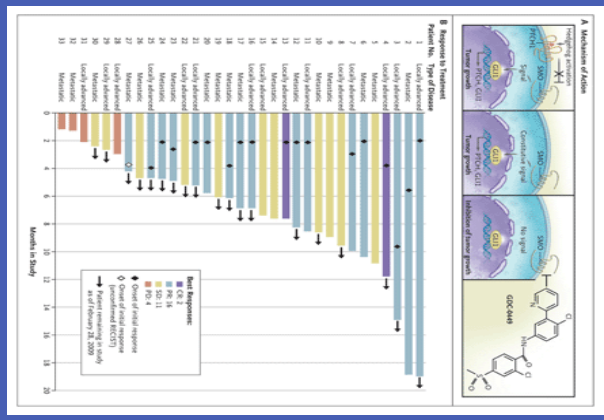
EML4-ALK fusion

Vemurafenib (BRAF inhibitor)



BRAF V600 mutation

GDC-0449 (Hedgehog inhibitor)



Basal Cell Carcinoma

- Lack of activity in biomarker +ve subpopulation treated at MTD may lead to "No GO" signal to halt development

Challenges of Enrichment Approach

- Screening for rare alterations
  - Sequential biomarker testing is inefficient
  - Patients who have exhausted standard treatment do not have time to wait for biomarker screening
- Many large academic institutions have started molecular profiling programs for matching patients to trial based on genotype
  - Testing and interpretation is complex
  - Not funded by public health care systems
  - Requires large portfolio of trials for matching
  - Tumor heterogeneity is problematic

Phase I Trials Risk/Benefit Ratio

- Response Rate 4-6% (first in human)
  - Higher for combination studies involved approved drug (~15%)
  - Majority of responses occur at 75-125% of recommended phase II dose
  - Response is a surrogate endpoint
    - Direct patient benefit is difficult to measure
- Risk of toxic death is low (<0.5%)

Pitfalls of Phase I Trials

- Maximum tolerated dose may not be appropriate for molecularly targeted agents
- Chronic toxicities usually cannot be assessed
- 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

Summary

- Phase I trials are critical for the evaluation of new therapies – translation from the lab to the clinic
- Patient safety/well-being is the most important principle in phase I
- Most drugs follow the MTD/RPTD paradigm
- Biomarker studies are essential to evaluate new cancer drugs
- Phase I trials are increasingly complex and require good team science