Prerequisites for Therapeutic Studies In Humans & Phase I Trials

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ddp BRAS DRUG DEVELOPMENT PROGRAM

Disclosures

- Research Funding (to Institution)
  - Astra Zeneca, BristolMyersSquibb, Genentech/Roche, GlaxoSmithKline, Merck, Nektar, Novartis, PTC Therapeutics, Sanofi, Seattle Genetics, Servier, SignalChem Life Sciences, Zymeworks
- Honoraria/Consultancy (to Institution)
  - Novartis, Pfizer, Roche, Sanofi

Overview

- Introduction to how new cancer drugs are tested in the clinic
  - Be acquainted with the preclinical studies required for an investigational drug therapy and the basis for selection of starting dose
  - Understand the purpose of phase I trials
  - Be familiar with concepts of dose limiting toxicities (DLTs) & recommended phase II dose (RPTD)
  - Discuss types of trial designs used determine the RPTD

The Traditional Drug Development Paradigm

Phase I	Phase II	Phase III
o Safety, tolerability o Pharmacokinetics o Pharmacodynamics o Preliminary antitumor activity	o Efficacy observed in selected tumor types, e.g. ORR, TTP, PFS	o Meaningful benefit obtained in a randomized setting against existent standard e.g. OS

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

The Drug

- Target
- Mechanism of Action
- Pre-Clinical Efficacy
- Pre-Clinical Safety
- Biomarker

The Target

- Biological Plausibility
  - Knock-in/Knock-out experiments
  - Role in disease pathogenesis
    - ie. Bcr-Abl, c-KIT, BRAF, etc
  - Expression in clinical specimens
    - Tumor types, prevalence, tissue specificity
    - All comers vs enriched design
    - Resistant vs naïve population
  - Prognostic/Predictive
  - Prior attempts to drug target

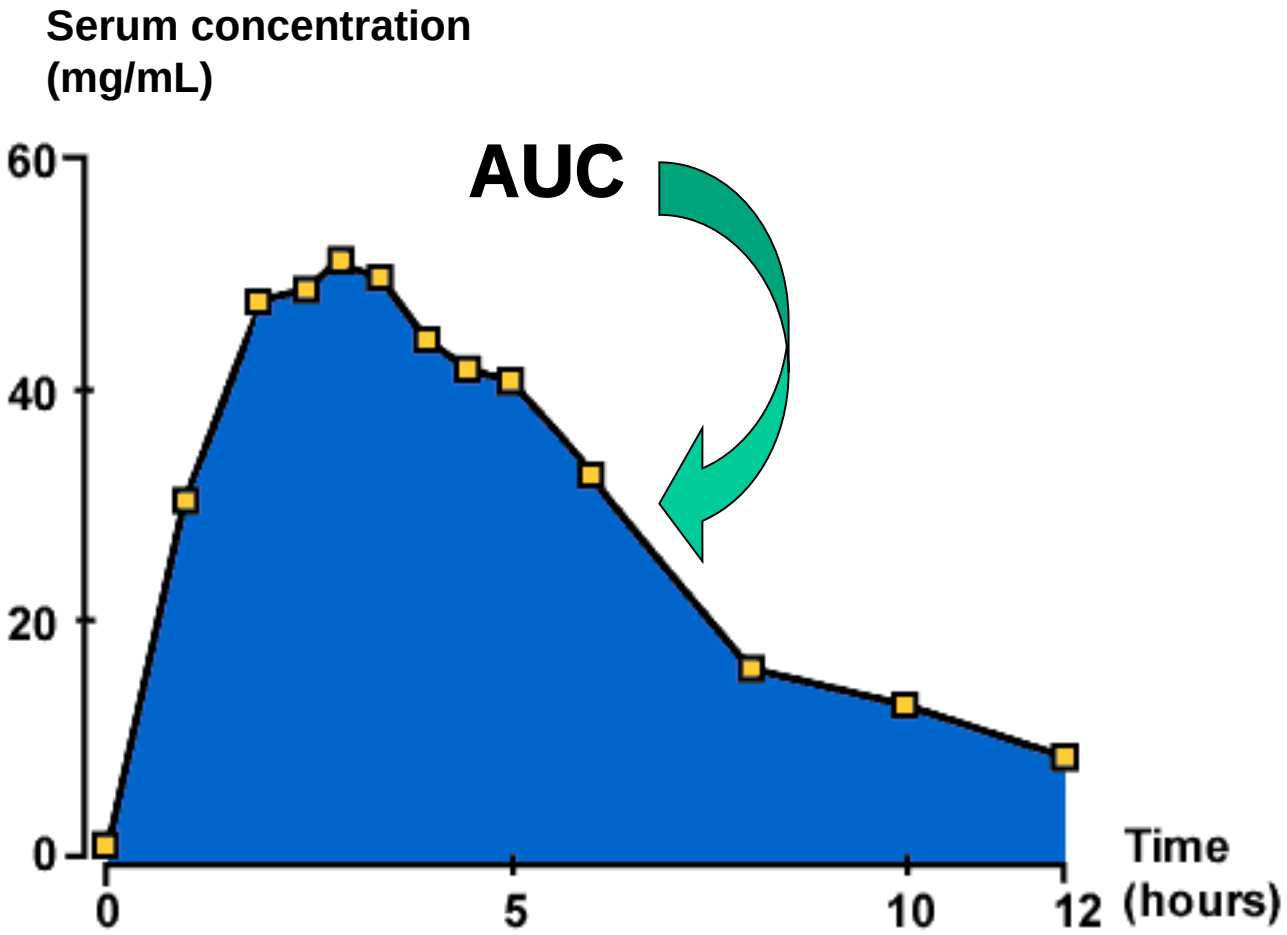
The Drug

- Production
  - Good Manufacturing Practice (GMP)
  - Sufficient quantities & practical dosage forms
- Chemistry
  - Small molecule, antibody, anti-sense, peptide, etc
- Absorption (PO/IV)
- Distribution (tissue concentration, reservoirs, BBB)
- Metabolism & Excretion
  - CYP enzymes, metabolites, route of excretion

The Drug

- Pharmacokinetic (PK) Profile
  - Maximum concentration (C_{max}), Exposure (AUC), Half-life ($T_{½}$), Distribution
  - Accumulation & multiple dose effects
  - PK-toxicity association
  - PK-efficacy association
- Impact on Trial Design
  - Route & schedule of administration
  - Eligibility criteria (renal & hepatic function)
  - Concomitant meds
  - PK/PD sampling time points

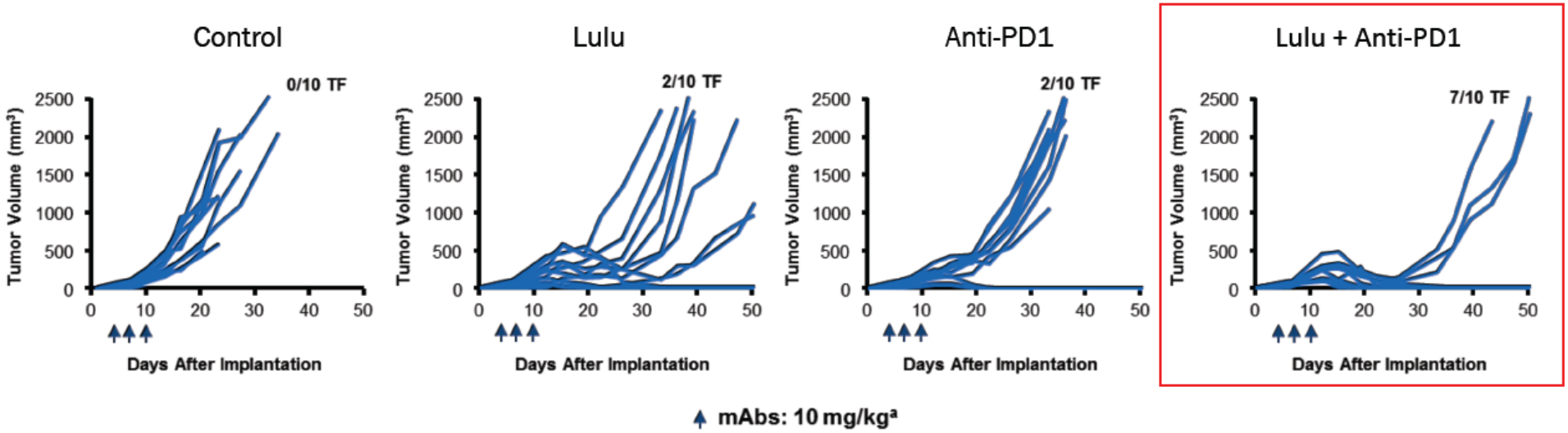
PK: Time x Concentration



Pre-Clinical Efficacy

- No mandated studies
  - Up to the company and investigators
- Not predictive of success
  - But high negative predictive value
- What to look for
  - Multiple xenograft models (>2)
  - Models with established tumors +/- mets before treatment (if applicable)
  - Regression rather than growth delay
  - IV or po administration
  - Dose response effects (and plasma drug levels)

Lululizumab: Novel IO Agent



Syngeneic Mouse Model

Courtesy of Lillian Siu

Pre-Clinical Toxicology

- Typically a rodent (mouse or rat) and non-rodent (dog or non-human primate) species
  - Monoclonal antibodies require cross-reactive species (ie. primate)
- Few animal organ specific toxicities predict for human toxicities
  - Myelosuppression and gastrointestinal toxicity more predictable
  - Hepatic and renal toxicities – large false positive

Starting Dose Considerations

LD10 (Lethal dose 10)

- Dose that is lethal in 10% of animals

NOAEL (NO observed adverse event level)

- The highest tested dose that has no harmful or adverse event in the animals

TDL (Toxic dose low)

- The lowest tested dose that caused any toxic effect in the animals

Minimum anticipated biological effect level (MABEL)

- Often used as starting dose for antibodies

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

Biomarker Assays

- Impact on Trial Design
  - Will it provide useful information (proof of mechanism or proof of concept)
    - Increased complexity & cost
    - Limited patient numbers
    - “Clinical Grade” assay
  - Patient selection
  - Serial tumor biopsies vs “surrogate” tissue
  - All comers vs expansion only

Objectives of Phase I Trial

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

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 cardiac risk
  - Recent hemorrhage or ongoing anticoagulation for agents with bleeding risk (ie. antiangiogenic)
  - Diabetes or fasting plasma hypergylcemia ≥ 7.0 mmol/L for agents with risk of hyperglycemia (ie. PI3K/AKT)

  Prohibited medications if significant risk of interaction with study drug

  Prior exposure to drug in same class

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 (ie. 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

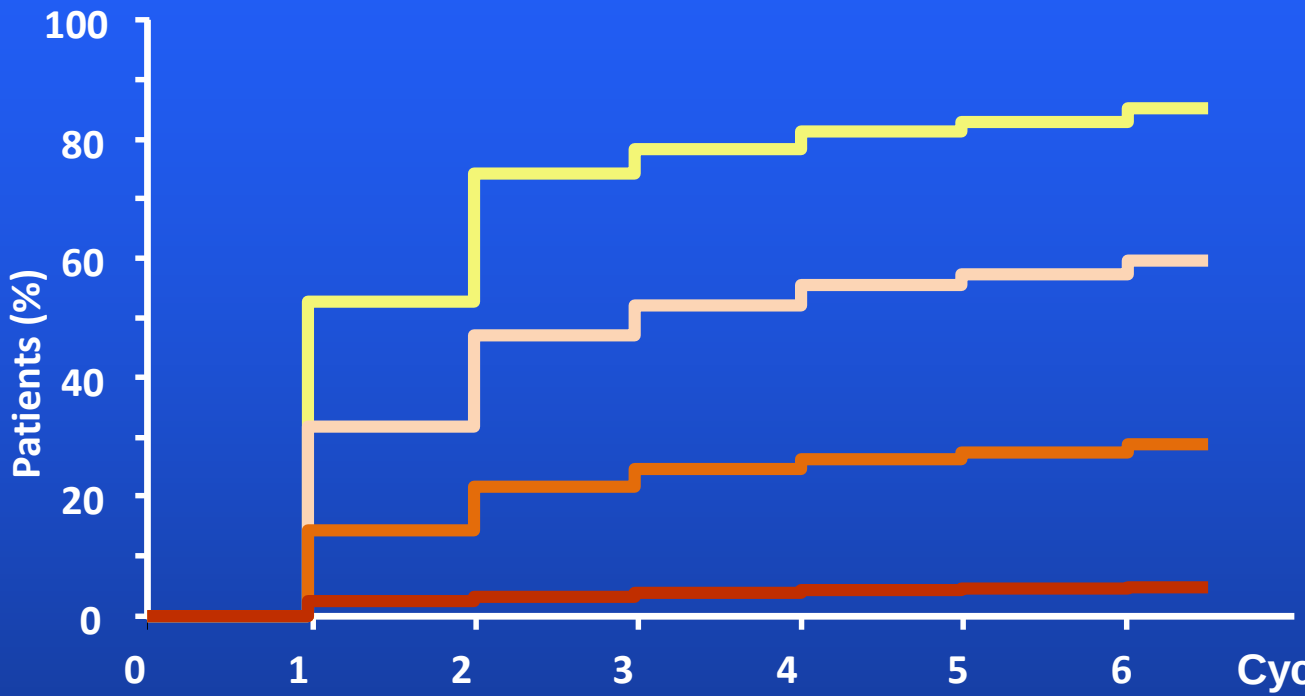
DLT Definition – Intermittent Dosing

- 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 x 109/L for > 5 or 7 days
  - Febrile neutropenia (ANC < 1 x 109/L, fever > 38.5□C)
  - Platelets < 25 x 109/L or thrombocytopenic bleeding
  - Inability to re-treat patient within 2 weeks of scheduled treatment

DLT Definition – Continuous 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)

Time to first toxicity



49.5 % of patients with G3-5 toxicities presented their first G≥3 toxicity after the first cycle.

These are not taken into account in the current DLT definition

Number of patients at risk :						N of events
2084	894	303	200	116	77	1776
2084	1264	534	375	212	154	1242
2084	1489	684	515	317	247	599
2084	1589	747	580	365	301	100

Grade >= 1
Grade >= 2
Grade >= 3
Grade >= 4

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 maximum tolerated dose

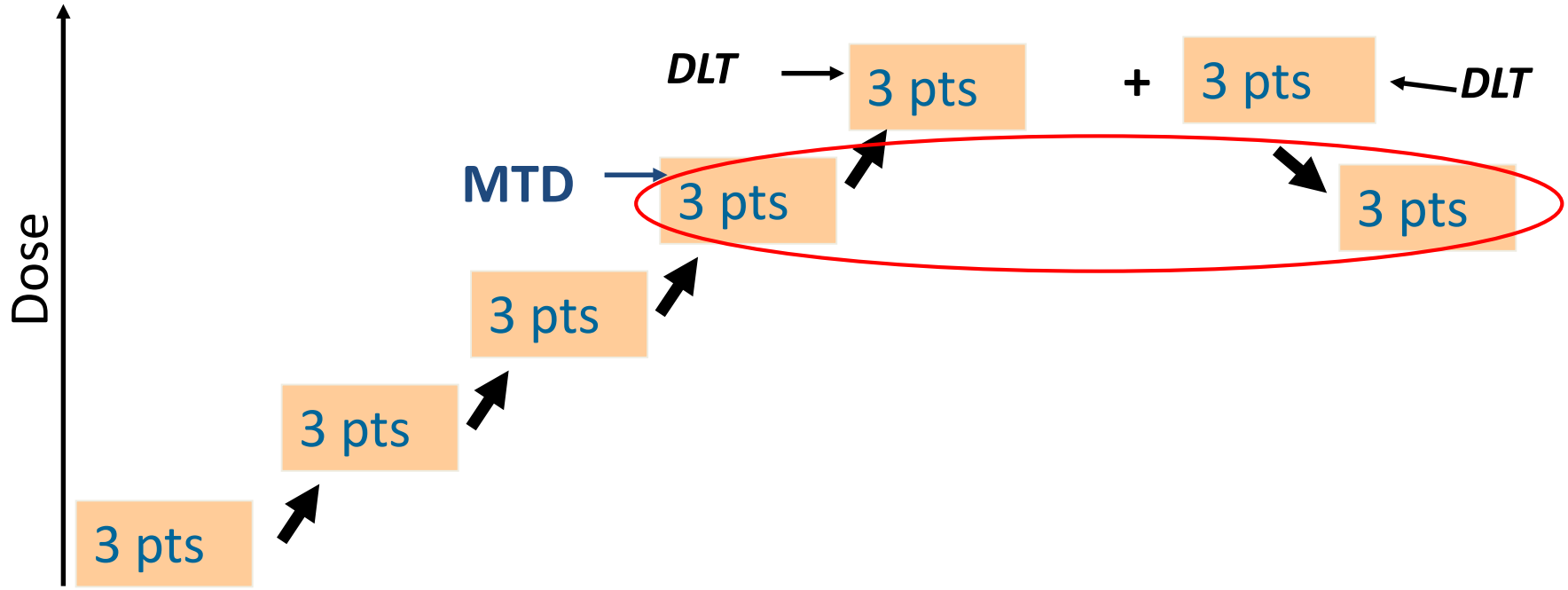
Recommended Phase II Dose

- 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

Traditional Phase I Testing Paradigm

⇧Dose = ⇧Likelihood of Efficacy

Classical 3+3 Design



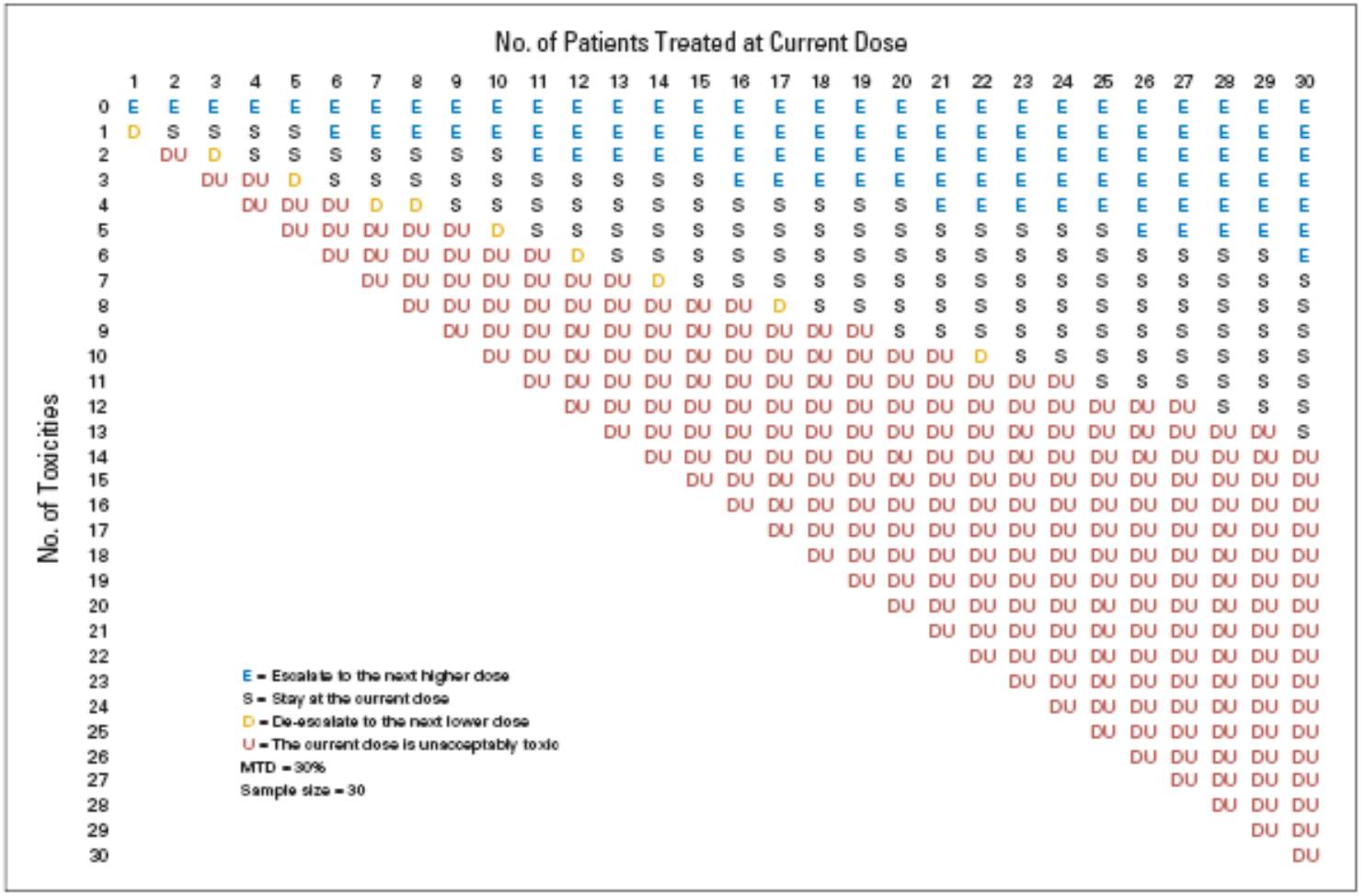
Problems with 3+3 Dose Escalation Design

- Wide confidence intervals around recommend phase II dose
- Patients treated in early dosing cohorts have very low drug exposure
- High risk of overdosing in later cohorts
- Dose escalation phase can be protracted

Accelerated Titration Design

- 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

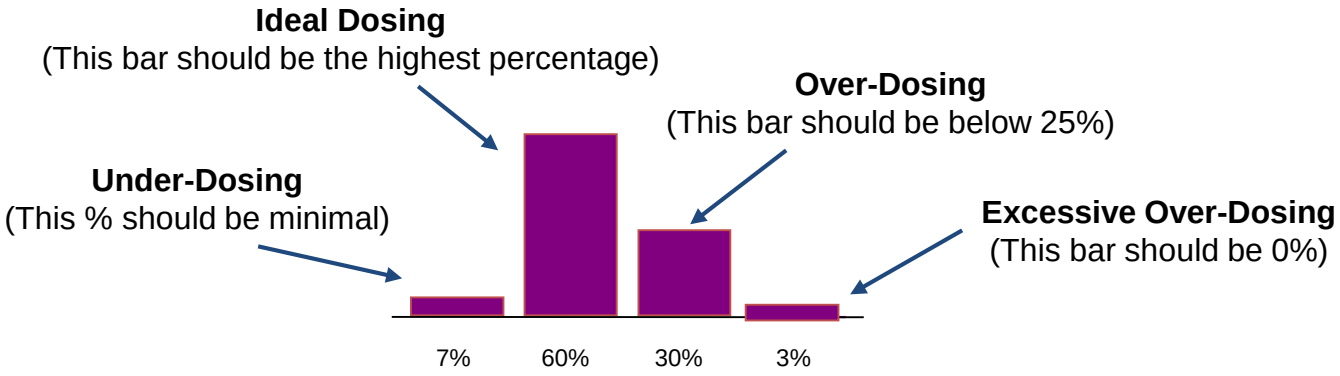
Modified Toxicity Probability Interval (mTPI) Design: An Adaptive Design



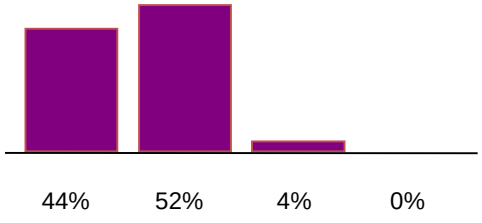
Ji Y and Wang S-Y. J Clin Oncol 31: 1785-1791, 2013

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

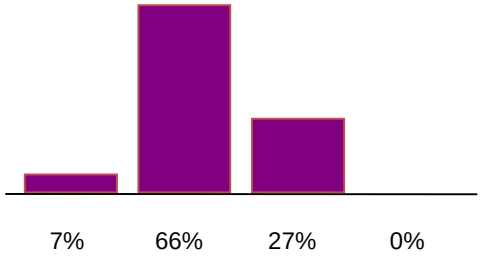
EXAMPLE of Probability of DLTs (Bayesian design)



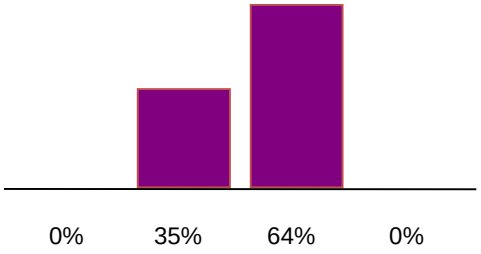
Drug at 0.5mg



Drug at 0.75 mg



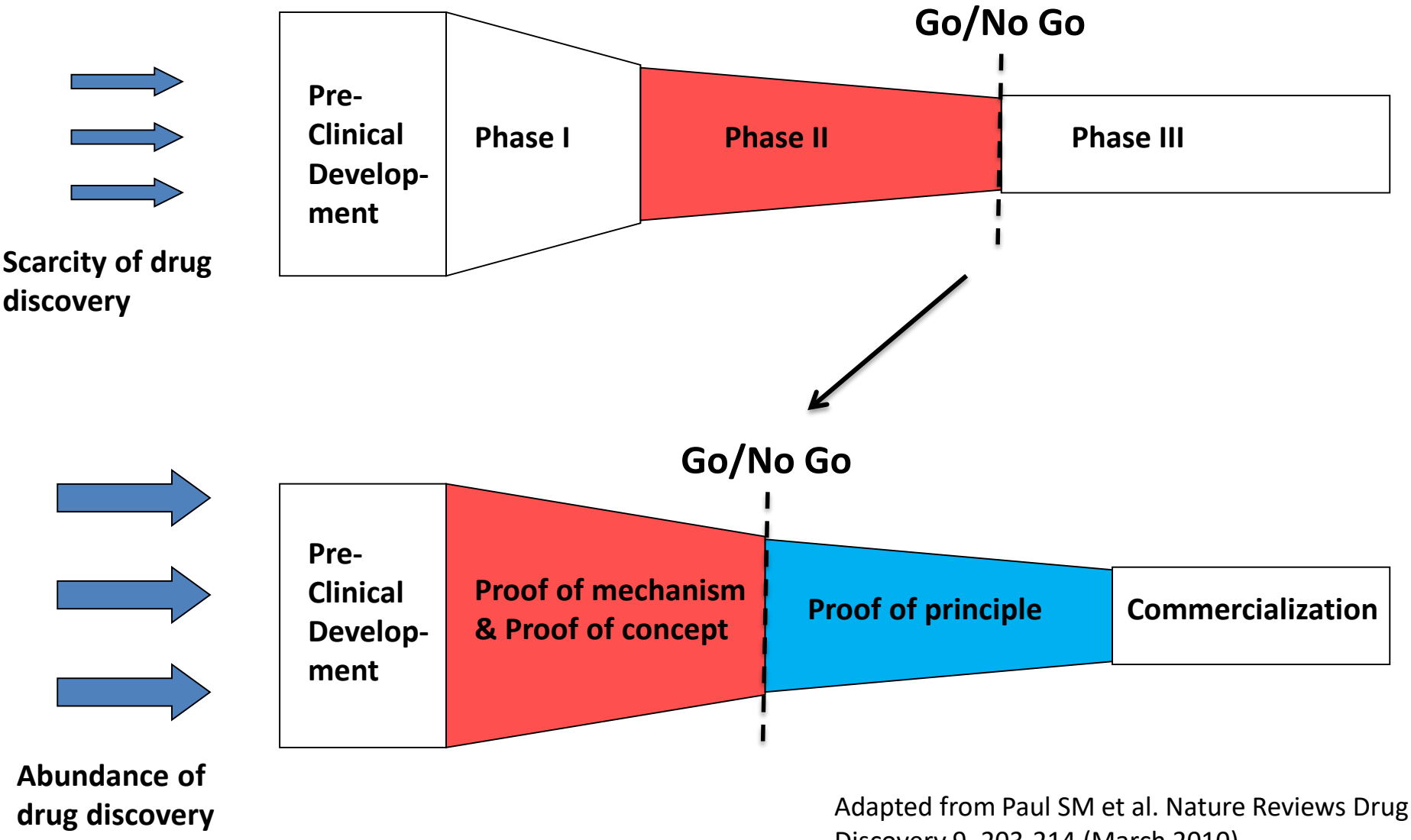
Drug at 1.0 mg



Limitations of Phase I Trials

- Chronic or cumulative toxicities usually cannot be assessed
- Uncommon toxicities will be missed
- Low likelihood of therapeutic benefit
    - Overall response rate = 5-10%
    - Majority of responses occur at 75-125% of recommended phase II dose
    - Low risk of toxic death (<0.1%)

Shifting Paradigm of Drug Development

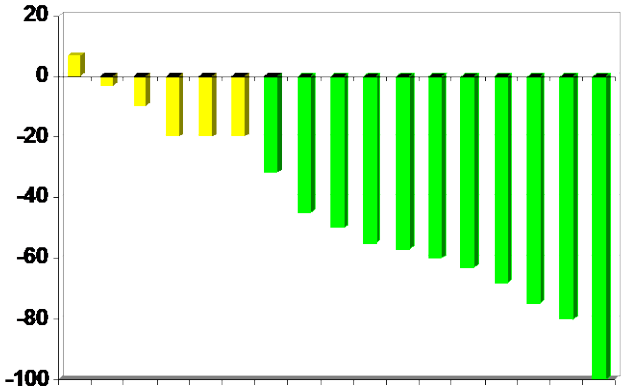


Adapted from Paul SM et al. Nature Reviews Drug Discovery 9, 203-214 (March 2010)

Enrichment Strategies

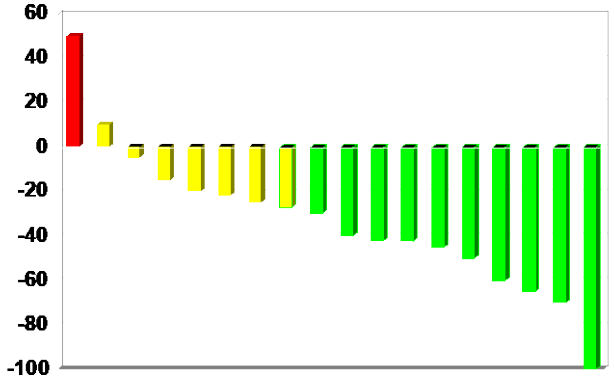
- Phase I trials with molecular enrichment

Vemurafenib (BRAF inhibitor)



BRAF V600 mutant melanoma

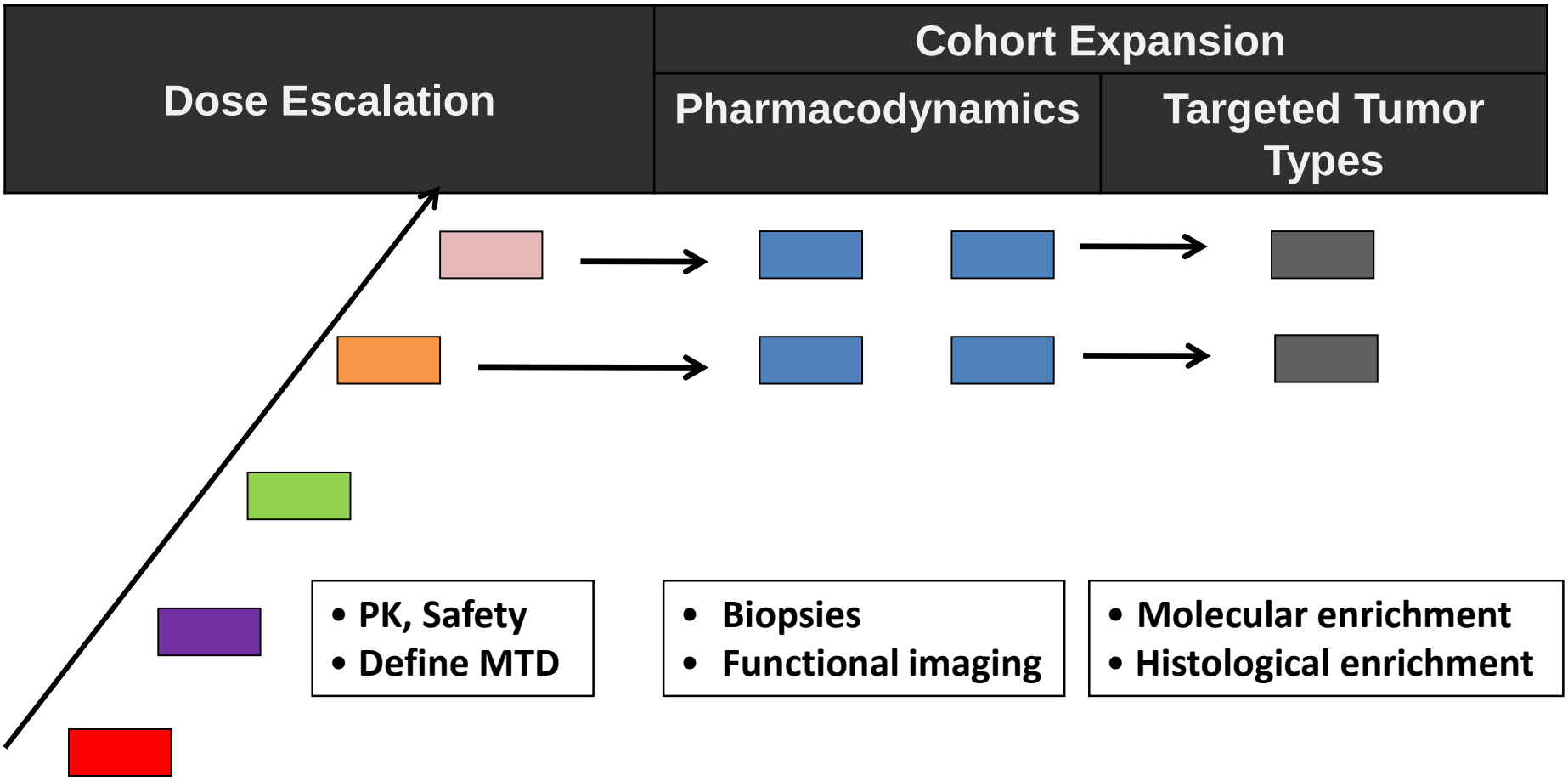
Crizotinib (ALK inhibitor)



EML4-ALK translocation NSCLC

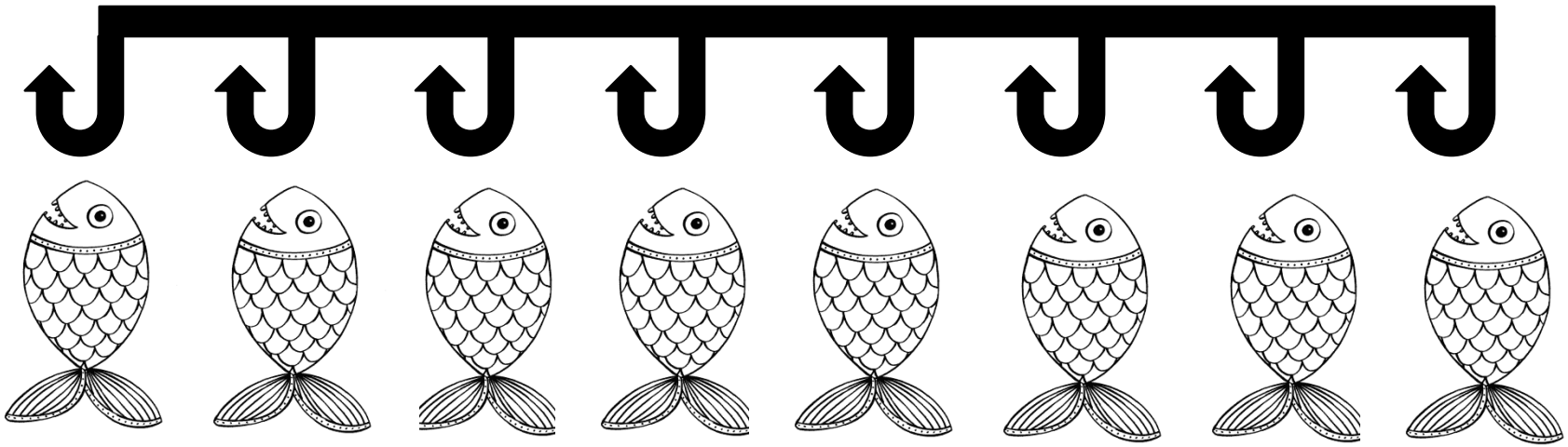
- Operational challenge of identifying patients with rare genomic alterations

“Seamless” Phase I/II Designs



Signal-Finding, Multiple Cohort Expansions

Common Design with Immune Checkpoint Inhibitors



Cancer A | Cancer B | Cancer C | Cancer D | Cancer E | Cancer F | Cancer G | Cancer H

Courtesy of Lillian Siu

Pros and Cons of Seamless Phase I-II Trials

Pros:

- Efficiency, time-saving
- Compelling data can lead to accelerated regulatory approval
- Frequent investigator-sponsor communications are critical to ensure safety

Cons:

- Often huge studies with 100s-1000s of patients – potentially exposing them to subtherapeutic or toxic doses
- Increased complexity often with multiple amendments
- Challenges in disseminating new safety information to investigators, IRBs, regulators in a timely manner
- Objectives, endpoints and statistical analysis plans often lacking
- Diluted clinical experience due to large number of participating sites

Adapted in part from FDA Draft Guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM616325.pdf

Take Home Messages

- Phase I trials are the interface between lab discoveries and clinical translation
- Patient safety/well-being is paramount
- 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